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Armand J. Quick and Clara V. Hussey, Milwaukee

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Mecamylamine, a New, Orally Effective, Hypotensive Agent
Edward D. Freis and Ilse M. Wilson, Washington, D. C.

A Rational Therapy of Systemic Lupus Erythematosus
N. B. Kurnick, Long Beach, Calif.

Peptic Ulcer and Pulmonary Emphysema
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Recognition and Treatment of the Various Seizure Disorders in Medical Practice
Lewis Levy and Edward Shanbrom, New Haven, Conn.

Review of Neuropsychiatry, 1955
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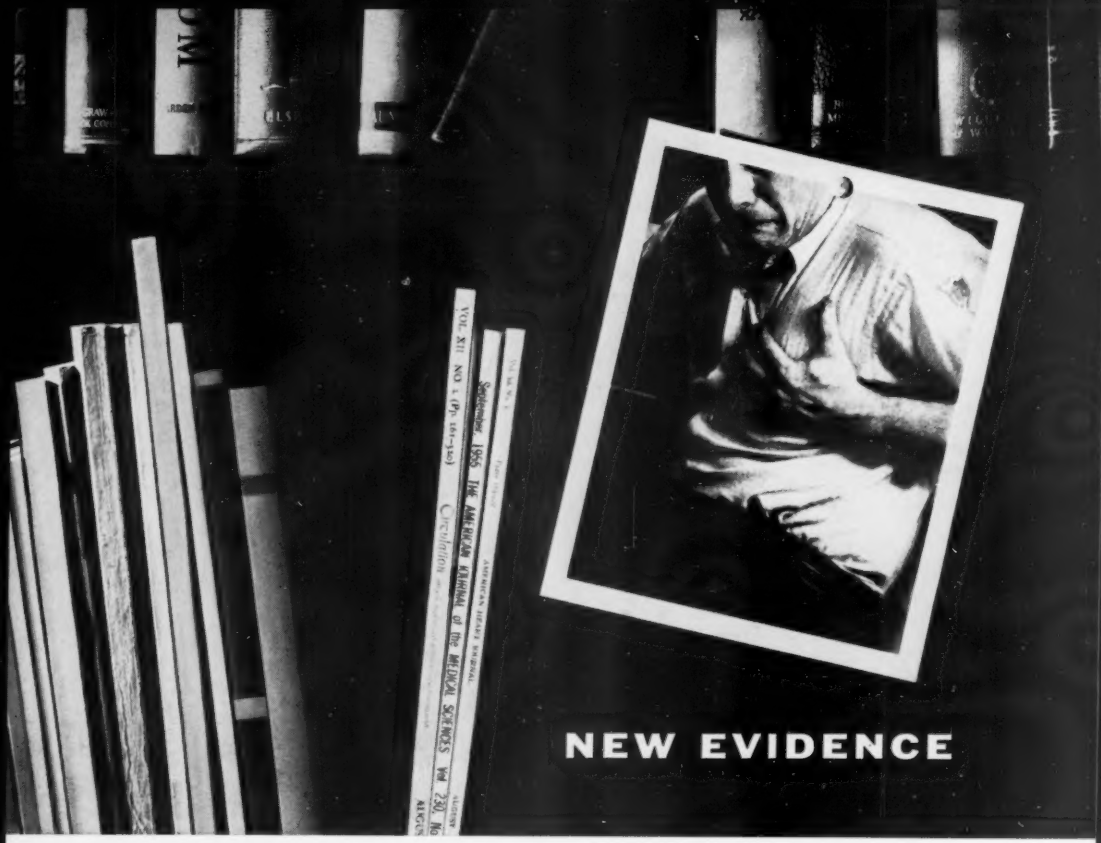

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TABLE OF CONTENTS

VOLUME 97 MAY 1956 NUMBER 5

EDITORIALS

PAGE

Polycythemia Vera 521

ORIGINAL ARTICLES

Hemophilia: Quantitative Studies of the Coagulation Defect
Armand J. Quick, M.D., and Clara V. Hussey, M.S., Milwaukee 524

A Roentgenographic Study of Skeletal Lesions in Sarcoidosis
George N. Stein, M.D.; Harold L. Israel, M.D., and Maurice Sones, M.D., Philadelphia 532

Idiopathic Paroxysmal Myoglobinuria
Leopold Reiner, M.D.; Nadya Konikoff, M.D., New York; Mark D. Altschule, M.D.; Gustave J. Dammin, M.D., and John P. Merrill, M.D., Boston 537

Mecamylamine, a New, Orally Effective, Hypotensive Agent
Edward D. Freis, M.D., and Ilse M. Wilson, M.D., Washington, D. C. 551

A Rational Therapy of Systemic Lupus Erythematosus
N. B. Kurnick, M.D., Long Beach, Calif. 562

Peptic Ulcer and Pulmonary Emphysema
Elliot M. Latts, M.D.; James F. Cummins, M.D., and Leslie Zieve, M.D., Minneapolis 576

A Contribution to the Philosophy of Medicine
Thomas S. Szasz, M.D., Bethesda, Md., and Marc H. Hollender, M.D., Chicago 585

Primary Atypical Nonbacterial Pneumonia
Lt. Robert L. Wolf (MC), U. S. N. R., and Cmdr. Loy T. Brown (MC), U. S. N. 593

TREATMENT IN INTERNAL MEDICINE

Recognition and Treatment of the Various Seizure Disorders in Medical Practice
Lewis Levy, M.D., and Edward Shanbrom, M.D., New Haven, Conn. 599

PROGRESS IN INTERNAL MEDICINE

Review of Neuropsychiatry, 1955
Stanley Cobb, M.D., Cambridge, Mass. 610

CASE REPORTS

Postdiphtheritic Polyneuritis and Pseudodiphtheritic Polyneuritis
H. J. Roberts, M.D., West Palm Beach, Fla. 618

Renal Disease, Inner Ear Deafness, and Ocular Changes
Ezra Sohar, M.D., Tel-Aviv, Israel 627

Follicular Lymphoma with Full Remission of Leukemic Phase
George J. Anday, M.D.; Henry L. Schmitz, M.D., and Louis R. Limarzi, M.D., Chicago 631

SCIENTIFIC EXHIBITS

Operations for Coronary Artery Disease
Claude S. Beck, M.D., and David S. Leighninger, M.D., Cleveland 639

BOOKS

Book Reviews 651

Books Received 658

News and Comment 660

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VOLUME 97 MAY 1956 NUMBER 5

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2. Finnerty, F. A., Jr.: The Value of Rauwolfia Serpentina in the Hypertensive Patient, Am. J. Med. *17*:629 (Nov.) 1954.
3. Cronheim, G., and Toekes, I. M.: Comparison of Sedative Properties of Single Alkaloids of Rauwolfia and Their Mixtures, Meet. Am. Soc. Pharmacol. & Exper. Therap., Iowa City, Iowa, Sept. 5, 1955.
4. Moyer, J. H.; Dennis, E., and Ford, R.: Drug Therapy (Rauwolfia) of Hypertension. II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension, A.M.A. Arch. Int. Med. *96*:530 (Oct.) 1955.

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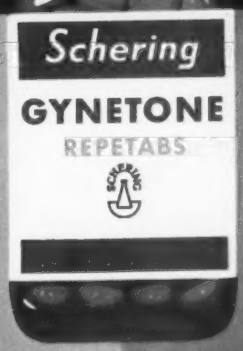

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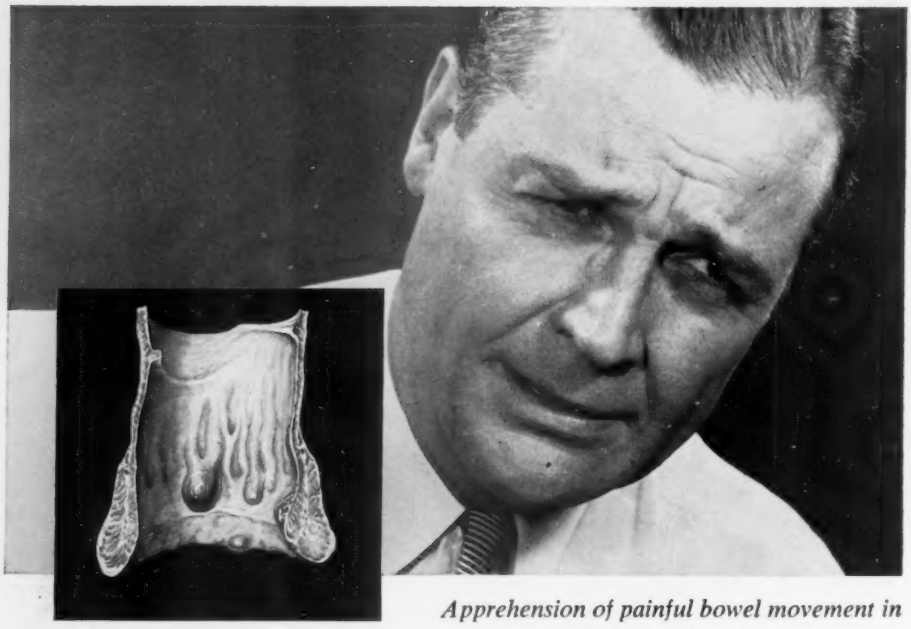

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*Soper, H. W.: Diseases of the Rectum and Colon: Their Diagnosis and Treatment, Am. J. Proctol. *4*:113 (June) 1953.

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A.M.A. Archives OF
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Editorials

POLYCYTHEMIA VERA

Current Status

POLYCYTHEMIA vera is one of the less unfortunate hematologic problems confronting the internist, for it is amenable to satisfactory control in a fair proportion of instances even though the cause of it is entirely unknown.

This disease is in a general category of myeloproliferative disorders. To this group also belong the myeloid leukemias, agnogenic myeloid metaplasia, and myelofibrosis with myeloid metaplasia. It has long been recognized that these conditions are somehow related. While excessive erythropoiesis is the major feature of polycythemia vera, there also may be mature or immature leucocytosis of the myeloid type in the peripheral blood. Occasionally, what appears to be early chronic myelocytic leukemia changes into typical polycythemia vera. In many cases, polycythemia vera eventuates in conditions in which erythropoiesis is quantitatively normal or subnormal, and the major feature is leucocytic abnormality.

In years past, this leucocytic abnormality was classed as "myelocytic leukemia," but as more nearly exact studies of bone marrow and potentially hemopoietic viscera have been carried on it has become apparent that in many cases the features are somewhat different: The potentially hemopoietic viscera contain foci of myeloid metaplasia rather than diffuse leukemic infiltration. In some of these cases there is actual fibrosis of the marrow, and hemopoiesis is accomplished largely in the spleen and liver.

Another hematologic development from polycythemia vera is acute leukemia. This may be an acute stem-cell type, an acute myelocytic type, or an acute erythroleukemia.

The role that therapy plays in these developments is not clear. Series of untreated patients with polycythemia vera are unknown. Phlebotomy was employed early as a form of treatment, and subsequently myelotoxic or hemolytic agents were used to contain the process of excess erythropoiesis. Within the past 15 years, radiophosphorus has come into favor, and low-voltage total-body irradiation has been employed to some extent.

Another feature that has tended to obscure hematologic sequelae of polycythemia vera is the high incidence of vascular accidents, such as thrombosis or hemorrhage, which tend to occur within the first years of the disease, whereas the hematologic sequelae come later. Since the widespread use of radiophosphorus

Submitted for publication Feb. 13, 1956.
Section of Medicine, Mayo Clinic, Rochester, Minn.

there has been better control of erythrocytic excess and high viscosity, with marked reduction of the incidence of vascular accidents, and the patients have lived into the period in which leukemia and myeloid metaplasia are common.

In a recent series * of 241 patients who had polycythemia vera, 3.3% died of acute leukemia, 3.7% died of other hematologic sequelae (probably myelofibrosis with myeloid metaplasia), and 6.2% were living (at the time of the study), but with anemia, leukemoid reaction, and gross splenomegaly, giving a total of 13.2% with hematologic sequelae. Occasional instances of these were reported in the literature prior to the advent of radiophosphorus therapy, and rare instances of acute leukemia are reported among untreated patients, but there is no major series for comparison with series such as the one mentioned above.

These disheartening considerations should not, however, obscure the fact that a considerable number of patients who have polycythemia vera enjoy good health for considerable periods of time after adequate therapy with radiophosphorus: This is particularly true of patients who do not exhibit marked leukemoid reactions in the peripheral blood and who do not have gross splenomegaly. In my experience, 76% of patients without leucocytosis in the peripheral blood obtained objective remissions lasting at least a year. Among patients with a mature leucocytosis, of more than 15,000 white cells per cubic millimeter in the peripheral blood, remissions were obtained for 69%. Among patients with marked leukemoid reactions the incidence of remission was 49%.

At this juncture, the ultimate fate of a statistically significant number of patients has not been determined, for the disease may be notoriously chronic, but patients who have had the disease for more than 15 years, with long periods of remission after therapy, are seen.

In our series there were 39 deaths. The mean age at death in those dying of hematologic sequelae was 62 years; in those dying of nonhematologic causes it was 64 years. In another series of 32 patients with polycythemia vera who had been treated by means other than radiophosphorus, the mean age at death was 54 years. This would suggest considerable salvage and extension of life expectancy in the group treated with radiophosphorus.

The classic polycythemic picture of ruddy cyanosis, splenomegaly, gross erythrocytic excess, and leucocytosis rarely offers any diagnostic problem. But, as more patients seek routine examination and good laboratory facilities become more available, unsuspected instances of erythrocytosis without leucocytosis or splenomegaly are uncovered.

Such erythrocytosis, particularly if it is not marked, poses a problem. Erythrocyte counts and hematocrit determinations are not infallible indications of a true polycythemic state. Elevated erythrocyte counts and hematocrit readings may occur when the total erythrocyte mass is normal but the plasma volume is reduced. This is often called "relative polycythemia." It may occur as a chronic condition without evidence of other disease, or it may appear in association with chronic vascular or neurologic disease.

Relative polycythemia must be clearly distinguished from mild polycythemia vera. At present, determination of the total erythrocyte volume is the most widely available method of such distinction. In the average laboratory this may be accomplished by determination of the plasma volume with use of the dye techniques.

* Stroebel, C. F.: Unpublished data.

The erythrocyte volume may then be inferred from the hematocrit reading. In laboratories equipped with facilities for radioisotope work, the erythrocyte volume can be determined directly by the use of techniques for labeling erythrocytes with radiophosphorus or radiochromium. When this has been done, the plasma volume can be inferred on the basis of the hematocrit reading or it can be measured independently with dye or radioisotopes.

In our experience, absolute erythrocyte volumes exceeding 60 cc. per kilogram of body weight (dye technique) are unequivocally within the range of true polycythemia. Values between 50 cc. and 60 cc. per kilogram are equivocal, and other evidence should be forthcoming if the diagnosis of polycythemia vera is to be established.

Studies carried out with radioiron (Fe^{59}) are of value when the condition at hand is equivocal. In the presence of true polycythemia radioiron is cleared from the plasma much more rapidly than normal. When "relative polycythemia" is present the clearance of radioiron from the plasma is normal.

Routine examination of specimens of bone marrow also may prove of value, but it must be kept in mind that procedures for the sampling of marrow may yield specimens which are indistinguishable from normal or which may even appear somewhat hypocellular. The excessive erythropoiesis of polycythemia vera may result from reactivation of areas of bone marrow which have been hemopoietically inactive in the normal state rather than from hyperplasia of areas of marrow in which hemopoiesis normally occurs. In many instances, however, the marrow will exhibit definite hyperplasia of erythrogenic or myeloid types.

Whatever the stimulus that causes polycythemia vera, it seems apparent that the disease may vary from a simple form which is readily controlled with radiophosphorus to one that involves granulocytic lines, metaplastic erythropoiesis and myelopoiesis, and resistance to radiophosphorus therapy.

CHARLES F. STROEBEL, M.D.

Hemophilia: Quantitative Studies of the Coagulation Defect

A Modified Prothrombin-Consumption Test Using Erythrocytin

ARMAND J. QUICK, M.D.
and
CLARA V. HUSSEY, M.S., Milwaukee

The prothrombin-consumption test described by one of us in 1947 [1] was based on the assumption that the amount of prothrombin remaining in serum when blood clotted under standardized conditions was a measure of the thromboplastin that resulted from the interaction of platelets with a plasma constituent which was designated as thromboplastinogen. It was concluded that the poor consumption of prothrombin observed when hemophilic blood clotted was caused by a lack of this plasma factor and that, therefore, the method could be employed for its assay. This assumption was supported by the significant increase in prothrombin consumption obtained after giving a hemophiliac a transfusion of normal blood or plasma. In mild hemophilia, however, the results were not always consistent, and, peculiarly, it was observed that when the platelet-rich plasma of such patients was clotted the prothrombin consumption was lower and more constant than when the test was done on whole blood.[2] This observation led to the discovery that the erythrocytes contain a potent clotting factor which is distinct from all the known primary clotting agents of the blood.[3] The name "erythrocytin" is proposed for this substance.

When the erythrocyte factor is added to normal plasma depleted of platelets, an exceedingly high consumption of prothrombin is obtained, which shows not only that the new agent can completely replace platelets but also that it is more potent than the latter. Strikingly, no measurable amount of prothrombin consumption occurs when an extract of hemolyzed erythrocytes (hemolysate) or a partially purified preparation of erythrocytin is added to the blood or plasma of a severe hemophiliac. When a purified preparation of thromboplastinogen is added to hemophilic blood or plasma and the prothrombin consumption with a fixed excess of hemolysate is determined, a straight-line proportion between the concentration of thromboplastinogen and the prothrombin-consumption time is obtained.[4] The possibility of utilizing this observation for the development of a method to assay blood for its concentration of thromboplastinogen was investigated, and the results of this study, especially as it pertains to hemophilia, are reported in this paper.

METHODS AND MATERIALS

Blood was collected with a silicone-coated syringe and needle and transferred to containers similarly coated which were immersed and kept in an ice bath.

The clotting time was carried out by standardized procedure previously described.[5] The normal range is 5 to 10 minutes.

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From the Department of Biochemistry, Marquette University School of Medicine.

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Prothrombin-Consumption Time (Unmodified)[6]

One milliliter of blood on which the clotting time had been determined was kept in the water-bath at 37 C for 15 minutes after clotting was completed; it was then centrifuged and reincubated 45 minutes longer. The prothrombin in the serum was determined by the one-stage method, with use of fresh rabbit plasma treated with $Ca_3(PO_4)_2$ as the source for fibrinogen and labile factor. The hemophilic range is 8 to 12 seconds except in very mild cases.

Prothrombin-Consumption Time with Added Heated Rabbit Brain Extract[7]

Blood, 1 ml., was mixed with 0.1 ml. of rabbit brain extract (heated for 20 minutes at 60 C), and the mixture was allowed to clot at 37 C. The subsequent steps were the same as in the unmodified test. The hemophilic range is 8 to 12 seconds. The name proposed for this test when originally described was "thromboplastinogen activity time" (TAT).

Prothrombin-Consumption Time with Added Aged Normal Serum

The test was carried out exactly as the preceding procedure except that 0.1 ml. of aged normal serum was used in place of the heated thromboplastin reagent. In true hemophilia the prothrombin-consumption time with stored serum remains the same as that obtained with the unmodified method, since thromboplastinogen is completely lacking.

Prothrombin-Consumption Time with Added Extract of Hemolyzed Erythrocytes

In place of heated thromboplastin reagent, 0.1 ml. of an extract of hemolyzed erythrocytes was mixed with 1 ml. of blood, after which the procedure is the same.

Preparation of Hemolysate (Extract of Hemolyzed Human Erythrocytes)[8]

The method of preparation which has been described is simple. It consists essentially of suspending carefully washed erythrocytes in saline solution and causing hemolysis by freezing the mixture at —20 C for 30 minutes. On thawing, an extract of lysed erythrocytes is obtained which has a high potency.

EXPERIMENTAL PROCEDURES

Estimation of Thromboplastinogen Level in Normal Blood

For estimation of thromboplastinogen level in normal blood fresh native hemophilic plasma was used as the assay medium. To a mixture containing 1 ml. of this plasma and 0.1 ml. of hemolyzed erythrocyte extract, varying amounts (ranging from 0.001 to 0.01 ml.) of fresh normal plasma adsorbed with $Ca_3(PO_4)_2$ were added, and the prothrombin-consumption time was determined. All the hemophilic plasmas used were from severe bleeders with clotting times longer than 40 minutes and with prothrombin-consumption times of 8 to 9 seconds, which were not corrected when normal aged serum was added to the blood before it clotted.

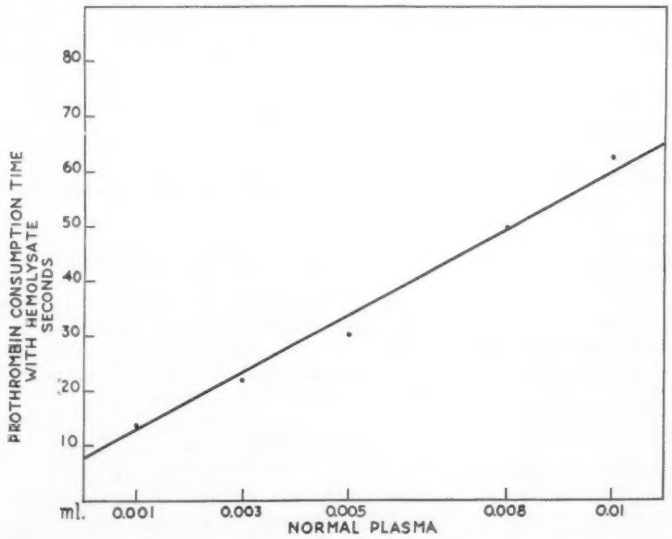

Fig. 1.—Assay of thromboplastinogen in plasma. Native hemophilic plasma, 1 ml., was mixed with 0.1 ml. of hemolysate, 0.001 ml. of aged serum, and varying amounts of the plasma to be assayed. The concentration of the resulting serum was determined by the standard method.[6]

This can be accepted as satisfactory evidence that these plasmas lack thromboplastinogen but contain the two accessory agents PTC and PTA (plasma thromboplastin component and antecedent), both of which are present in the serum. When the amount of added normal plasma is plotted against the prothrombin-consumption time, a straight line is obtained (Fig. 1). This agrees with the previous finding,[4] in which a similar curve is obtained by adding purified thromboplastinogen in increasing amounts to hemophilic plasma. It is to be noted that 0.001 ml. of normal plasma increases the prothrombin-consumption time from 9 to 13 seconds. It can be assumed that the increase in prothrombin consumption resulting from the addition of the plasma to be tested in amounts ranging from 0.001 to 0.01 ml. is due solely to the thromboplastinogen content and that the hemophilic plasma serving as the assay medium supplies a sufficient quantity of the other factors, such as PTC and PTA, which also are part of the thromboplastin complex. The straight-line relationship between the amount of plasma added and the prothrombin-consumption time may be regarded as support for this assumption.

TABLE 1.—*Comparative Concentrations of Thromboplastinogen in the Bloods of Normal Persons and of Hemophilic Carriers*

	Plasma Sample, Ml.	Prothrombin Consumption with Hemolysate Added, Seconds
Hemophiliac I*	1.000	25
Normal Subject A	0.005	..
Hemophiliac I	1.000	32
Carrier 1	0.005	..
Hemophiliac II*	1.000	30
Normal Subject A	0.005	..
Hemophiliac II	1.000	28
Carrier 2	0.005	..
Hemophiliac III*	1.000	31
Normal Subject A	0.005	..
Hemophiliac III	1.000	25
Carrier 3	0.005	..

* The clotting times of the three hemophiliacs were 48, 64, and 60 minutes, respectively, and the prothrombin-consumption time with hemolysate added was 9 seconds.

The plasma thromboplastinogen concentration was determined on a small number of normal subjects and also on two hemophilic carriers. Instead of using a series of dilutions, only one fixed quantity, namely, 0.005 ml., was added to 1 ml. of hemophilic plasma. The results are recorded in Table 1.

Effect of Transfusions on the Thromboplastinogen Level of the Blood and Its Duration

The results reported in Table 2 were obtained on patients who either were given a transfusion to control bleeding or were prepared for an operation. Only three observations are recorded, since the findings are typical of those observed whenever a true hemophiliac is given a fresh blood or plasma transfusion.

TABLE 2.—*Effect of Transfusion on Clotting Tests in Hemophilia*

	Transfusion		
	Before	Immediately After	After 24 Hr.
Case 23, age 4, 350 ml. fresh frozen plasma			
Clotting time, min.	21	6	7
Prothrombin-consumption time, sec.	8½	14	15½
Thromboplastinogen-activity time, sec.	9	12	14
Hemolysate test,* sec.	9	71	33
Case 22, age 6, 250 ml. fresh frozen plasma			
Clotting time, min.	30	6	..
Prothrombin-consumption time, sec.	9	13	..
Thromboplastinogen-activity time, sec.	9	12	..
Hemolysate test,* sec.	9	95	..
Case 1, age 29, 500 cc. fresh frozen plasma			
Clotting time, min.	63	7½	8
Prothrombin-consumption time, sec.	8	13	11
Thromboplastinogen-activity time, sec.	8	10½	11
Hemolysate test,* sec.	9	54	35
250 cc. fresh frozen plasma and 500 cc. fresh blood			
Clotting time, min.	60	5½	..
Prothrombin-consumption time, sec.	8	20	..
Thromboplastinogen-activity time, sec.	8	17	..
Hemolysate test,* sec.	8	81	..

* Prothrombin-consumption time with added extract of hemolyzed erythrocytes.

Clinical and Experimental Findings in Fifty Hemophiliacs

In the selection of the cases, all PTC and PTA (plasma thromboplastin component and antecedent) deficiencies as well as those in which the diagnosis was uncertain were excluded. In most instances the patient was studied at least twice.

Constancy of the Hemophilic Defect in a Family

Five hemophiliacs, distantly related, who could trace their inheritance to a common carrier five

TABLE 3.—*Laboratory and Clinical Data on Fifty Cases of Classical Hemophilia*

Patient	Family	Relationship*	Year of Birth	Clotting Time, Minutes	Prothrombin-Consumption Time, Seconds				Clinical Data					
					Basic	TAT†	Hemolysate Added	Serum Added	Hereditary History	Hemarthrosis	Hematuria	Epistaxis	Transfusions, No.	Bleeding Tendency
1	1	N	1925	63	8	9	9	9	+	+	+	−	>10	++++
2	..	U	1898	90	9	9	9	9	+	+	+	−	>10	++++
3	2	B	1949	63	9	8½	9½	9	+	+	−	−	>10	++++
4	..	B	1951	45	9	9	9	9	+	−	−	−	..	++
5	3	..	1920	60	8	8	9	9	+	+	+	−	>10	++++
6	4	..	1911	37	8	8	8	8	+	+	+	−	>10	+++
7	5	..	1937	60	8	8	8	9	+	+	+	+	>10	++++
8	6	B	1946	40	9	9	9½	9	+	+	−	+	>10	+++
9	..	B	1940	35	9	9	9	9	+	+	−	+	<10	+++
10	7	..	1940	25	9	9½	10	9	−	+	−	−	>10	+++
11	8	..	1917	53	8	8½	8	8	+	+	−	−	>10	++++
12	9	..	1946	60	8½	8½	8½	8½	−	+	−	−	<5	+++
13	10	..	1954	50	8	8½	8	8	..	+	−	−	..	+++
14	11	..	1923	43	8½	8½	8½	9	+	+	+	−	>10	++++
15	12	..	1921	42	8	9	9	9	−	+	+	+	>10	++++
16	13	..	1921	42	8	9	9	9	+	+	+	−	>10	++++
17	14	..	1952	45	8	8½	8	10	+	−	−	−	..	+++
18	15	..	1905	64	8	8½	9	9	+	+	−	+	>10	++++
19	16	..	1945	79	8½	8½	8	9	−	+	+	+	>10	++++
20	17	..	1950	60	8	8½	8½	8½	..	+	+	−	>10	++++
21	18	..	1948	70	8½	8½	8½	8½	−	+	−	−	>5	++
22	19	B	1949	89	9	9	9	9	+	−	−	−	5	++
23	..	B	1951	50	8½	9	8½	8½	+	−	−	−	5	+++
24	20	..	1952	30	8½	8½	8½	8½	+	+	−	+	>10	++++
25	21	..	1937	60	9	9½	9	9	+	+	+	−	<5	+++
26	22	..	1952	40	8	8½	8	8	+	+	−	−	>5	+++
27	23	..	1944	80	8½	9	9	8	−	+	+	+	>10	++++
28	24	..	1942	78	9	10	8	8	+	+	−	+	..	++++
29	25	..	1951	38	8	10½	9	9	−	−	−	−	>10	+++
30	26	..	1942	48	9	8	11	9	+	+	+	..	>10	++++
31	27	..	1943	50	9	9	9	9	−	+	−	+	>10	+++
32	28	..	1945	60	8	9	9	8½	−	+	+	−	>10	++++
33	29	..	1948	55	8	8	8	9	−	+	−	−	>10	++++
34	30	C	1946	17	9	9	..	9	+	+	−	−	>10	++++
35	..	C	1945	19	10	10	16	10	+	+	−	−	>10	++++
36	31	..	1917	25	8	12	18	9	+	+	+	−	>10	+++
37	32	..	1923	25	9	9	19	9	−	+	+	−	>10	+++
38	33	..	1947	22	9	9½	30	9	−	+	−	−	>5	+++
39	34	..	1919	20	8	8	16	8	+	+	−	−	2	++
40	35	C	1925	24	9½	9	20	9	+	+	+	−	>10	+++
41	35a	B	1942	16	11	11	25	10	+	+	+	..	>10	+++
42	..	B	1944	16	11	11	23	10	+	+	+	..	>10	+++
43	35b	B	1938	18	9	9	22	9	+	+	−	−	..	+++
44	..	B	1934	16½	8	8	18	8½	+	+	+	−	>10	+++
45	36	B	1952	11	12	10	25	10	+	−	−	−	<5	++
46	..	B	1953	14	11½	10	30	10	+	−	−	−	..	+
47	37	C	1938	8	19	9½	21	16	+	−	−	−	<5	++
48	..	C	1932	9½	19	9½	20	12	+	−	+	−	1	+
49	..	C	1936	11	15	9½	20	13	+	−	−	−	..	+
50	..	C	1932	8	15	12	27	14	+	−	−	−	>5	++

* N, nephew; U, uncle; B, brother; C, cousin.
† Thromboplastin activity time.

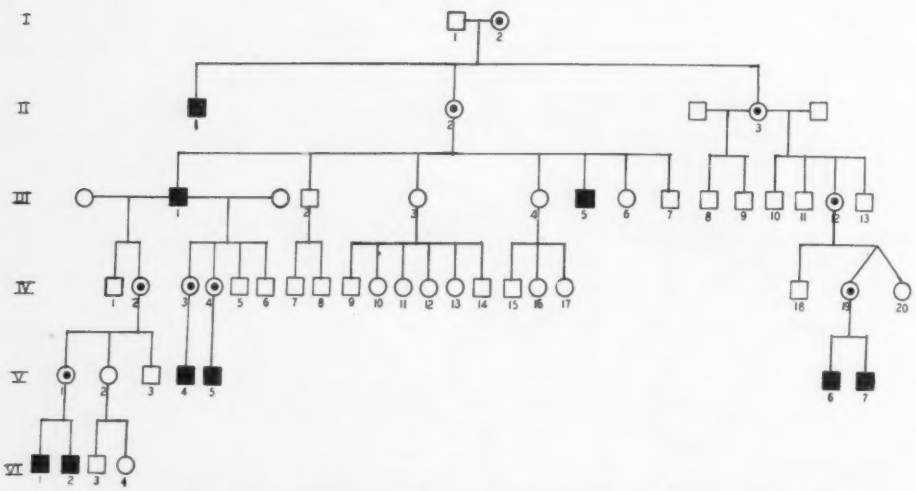

Fig. 2.—Pedigree of hemophilia. Subject V, 5 is Patient 40 in Table 3; Subject V, 6 is Patient 43; Subject V, 7 is Patient 44; Subject VI, 1 is Patient 41, and Subject VI, 2 is Patient 42. All have a clotting time in the range of 18 to 24 minutes and a prothrombin-consumption time of 9 to 10 seconds (basic) and 18 to 25 seconds with hemolysate.

and six generations removed were studied. The findings are recorded in Table 3, and the pedigree, in Figure 2.

COMMENT

Progress in the study of hemophilia has run fairly parallel to the development and improvement of methods to study quantitatively the defect of the disease. The unmodified prothrombin-consumption test, which is based on the amount of prothrombin remaining in the serum when blood is clotted under standardized conditions, is satisfactory when the depletion of thromboplastinogen is very marked, as in severe hemophilia, but becomes less accurate in the mild cases. By addition of an excess of platelet extract, the test is improved in specificity and, to some extent, in sensitivity but not sufficiently to obtain satisfactory results in the extremely mild cases of hemophilia. It has been difficult to distinguish between the normal and mild hemophilia, since both the clotting time and the prothrombin-consumption time are normal.[2]

The finding that the erythrocyte contains a clotting factor which can completely replace the platelet factor but requires thromboplastinogen for its activity has made it possible to develop a test which measures the thromboplastinogen of the blood with more precision than has hitherto been possible. The finding that when an excess of the erythrocyte factor is present the prothrombin-consumption time is a straight-line function of the concentration of thromboplastinogen makes it possible to determine with relative ease the thromboplastinogen concentration of both normal and hemophilic blood.

Plasma from a severe hemophiliac serves as the assay medium, since its thromboplastinogen concentration is practically zero. The addition of 0.001 ml. of normal plasma to 1.0 ml. of hemophilic plasma is enough to increase the prothrombin-consumption time from the base value of 8 (or 9) to 13 seconds. This demonstrates that the method can determine accurately values less than 0.1% of normal. The addition of 0.005 ml. of normal plasma to 1 ml. of hemophilic blood results in a prothrombin-consumption time of about 30 seconds. It is significant that two carriers who were among the group studied had as high a concentration of thromboplastinogen as normal subjects, which makes the possibility of detection of carriers appear more

remote than ever. It is to be noted that a considerable number of hemophiliacs have a prothrombin-consumption time of 20 to 30 seconds when hemolysate is added. This suggests that they have about 0.5% as much thromboplastinogen as the normal average. Hemophiliacs whose prothrombin-consumption time exceeds 30 or 40 seconds are almost always found to be mild bleeders. It appears, therefore, that a level of 1%, or perhaps a little more, assures fairly good hemostasis. This is in marked contrast to the requirement of prothrombin for hemostasis, since when its concentration is 30% a bleeding tendency becomes manifest.[8]

One of the interesting observations recorded in Table 3 is that when the clotting time is shorter than 25 minutes a measurable amount of prothrombin consumption can be shown by the new test. When the clotting time is longer than 25 minutes neither the hemolysate test nor, perhaps, any other modification of the prothrombin consumption is delicate enough to detect and measure the thromboplastinogen. When the latter is added in increasing amounts to severe hemophilic blood, the clotting time returns to normal much sooner than the prothrombin-consumption time. This explains why a normal clotting time does not exclude the diagnosis of mild hemophilia.

Information concerning the plasma level of thromboplastinogen at which hemostasis is effected is of utmost importance in treating hemophilic bleeding and in preparing the bleeder for an operation. Experience has shown that a transfusion of 500 ml. of fresh plasma is enough to prepare an adult hemophiliac for the extraction of several teeth or even for a major operation.[10] The results of the present study demonstrate that even after 24 hours the beneficial effect is not wholely dissipated. In several cases more than 0.5% was still present after 24 hours. The findings agree in the main with those of Brinkhous and his associates * except in the actual percentage figures of thromboplastinogen concentration. They estimate the concentration in moderately severe hemophlia to be $<3\%$ and in mild hemophilia, 16%. The present results suggest $<1\%$ and 5%, respectively, or in other words, only one-third of their values. These investigators also noted the marked rise in thromboplastinogen of the plasma immediately after transfusions. They found, however, that after 6 hours the effect could no longer be measured by the partial thromboplastin time (PTT) or their antihemophilic factor (AHF) assay method, whereas their prothrombin-utilization test showed no decrease in 24 hours.

The severity of the bleeding tendency in hemophilia is clearly related to the laboratory findings and, specifically, to the quantitative deficiency of thromboplastinogen. One may roughly divide cases of hemophilia into (1) the severe cases, in which the thromboplastinogen is too low to be measured and the clotting time is over 25 minutes; (2) the moderately severe cases, in which the thromboplastinogen concentration is about 0.5% and the clotting time is 12 to 25 minutes, and (3) the mild cases, with a thromboplastinogen concentration of 0.5% to 1% and a normal or only slightly prolonged clotting time. In the severe hemophiliac, hemarthrosis is common and usually some ankylosis of the joint occurs if it is left untreated. Bleeding into the joint may occur, however, even in mild cases, but spontaneous and complete recovery is the rule. A rigid comparison between laboratory findings and the clinical picture is not possible, because much of the bleeding is due to superimposed influences. A hemophilic child, for example, who is protected against trauma is less apt to have numerous joint involvements. This is illustrated by the rarity of hemarthroses in babies before they begin to crawl or walk.

All the cases recorded in Table 2 may be regarded as true hemophilia. In none is the defect corrected by the addition of aged serum, which contains both PTC and PTA (plasma thromboplastin component and antecedent). This may be regarded as fairly satisfactory evidence that none of the cases lacked these two factors. It should be noted

* References 11 and 12.

that good and consistent agreement between the clotting time, prothrombin-consumption time, and the modified test with added hemolysate is obtained. Whenever the agreement between these three tests is poor, as for instance a very prolonged clotting time with only a moderately abnormal prothrombin-consumption time, the possibility of a bleeding disease other than hemophilia should be investigated. It will be noted that the TAT test is very sensitive to detect mild hemophilia but it is unsatisfactory to distinguish between the mild and severe cases.

The data presented in Table 2 can be considered to be fairly representative of hemophilia in the United States, since the cases included are from various sections of the country but predominantly from the Midwest. The ratio of severe to mild cases is not accurate, since many of the mild hemophiliacs do not make any effort to seek medical advice and, therefore, go unnoticed. Two Negro boys who have two normal brothers are among the fifty cases studied. This is probably a fairly representative ratio of the incidence of the disease in Negroes as compared with whites. Only two Jewish hemophiliacs were studied, which also suggests a somewhat lower incidence in this group than in the population as a whole. It should be noted that some of the severe hemophiliacs are over 30 years old, while two were diagnosed before they were 6 months old.

It will be observed in Table 2 that the affected members of any one family are strikingly similar. This is in accordance with the results obtained in a previous study of five families reported in 1952.[2] It was concluded at that time that "the transmission of the hemophilic defect appears to be quantitative, that is: all the affected sons of a carrier are alike both clinically and in the clotting defect." Merskey [13] had arrived at a similar conclusion and, more recently, Graham and his co-workers [14] have described a family in which all affected members are mild bleeders.

With the development of the modified consumption test using hemolysate, a more precise means for studying the quantitative inheritance of the hemophilic defect becomes possible. This was further fostered by the fortunate discovery of a hemophilic family in the community which permitted a thorough study of its affected members and made it possible to obtain an accurate pedigree through six generations. It will be noted that the disease can be traced to a carrier (I, 1) who had a hemophilic son and two carrier daughters. Two great-great-grandchildren and one great grandchild of the older daughter (II, 2) and two great grandchildren of the younger daughter (II, 3) have been repeatedly studied, and all have been found strikingly similar. In every affected member studied, the clotting time has remained in the range of 16 to 24 minutes and the prothrombin-consumption and thromboplastinogen activity times have stayed nearly identical. All affected members of this family have a remarkably constant concentration of thromboplastinogen as measured by the hemolysate test. In one, the thromboplastinogen was elevated by a transfusion of fresh frozen plasma to 58 seconds but within a few days it returned to the basic value of about 20 seconds.

The pedigree clearly illustrates that the hemophilic defect, namely, the deficiency of thromboplastinogen, remains quantitatively unchanged regardless of the number of generations through which it passes or the sex which transmits it. The quantitative constancy of the hemophilic defect in a family has been observed frequently enough to have the force of a law. From the pedigree presented, it seems obvious that the incidence of hemophilia in a family can only be reduced by dilution, since only one-half the children of a carrier inherit the defective gene. If the affected male marries and has offspring, the incidence is theoretically doubled, because all his daughters are carriers.

SUMMARY

A new test is described for the quantitative estimation of the thromboplastinogen concentration of the blood. It is based on the principle of the prothrombin-consumption

procedure modified by the addition of an extract of hemolyzed erythrocytes, and plasma from a severe hemophiliac is used as the assay medium. The method is sensitive to concentrations of thromboplastinogen less than 0.1% of normal.

In severe hemophilia only a trace of thromboplastinogen is present in the blood and, even at a level of 0.5%, the bleeding tendency is severe. A fairly close relationship between the concentration of thromboplastinogen, the clotting time, and the severity of the bleeding state exists. A transfusion of fresh blood or plasma can elevate the level of thromboplastinogen in a hemophiliac sufficiently to effect fairly normal, though temporary, hemostasis. Although the thromboplastinogen disappears fairly rapidly from the blood, as much as 0.5% or more often remains after 24 hours following a single transfusion of 500 ml. in an adult.

The laboratory and clinical findings in 50 hemophiliacs are summarized. Evidence is presented that the degree of the hemophilic defect is quantitatively transmitted and that the intrinsic severity of the disease is the same in all the affected members of a family.

REFERENCES

1. Quick, A. J.: Studies on the Enigma of the Hemostatic Defect in Hemophilia, Am. J. M. Sc. **214**:272, 1947.

2. Quick, A. J., and Hussey, C. V.: Hemophilia: Clinical and Laboratory Observations Relative to Diagnosis and Inheritance, Am. J. M. Sc. **223**:401, 1952.

3. Quick, A. J.; Georgatsos, J. G., and Hussey, C. V.: The Clotting Activity of Human Erythrocytes: Theoretical and Clinical Implications, Am. J. M. Sc. **228**:207, 1954.

4. Georgatsos, J. G.; Hussey, C. V., and Quick, A. J.: Nature and Action of a New Clotting Factor Obtained from Erythrocytes, Am. J. Physiol. **181**: 30, 1955.

5. Quick, A. J.; Honorato, R. C., and Stefanini, M.: The Value and Limitations of the Coagulation Time in the Study of the Hemorrhagic Diseases, Blood **3**:1120, 1948.

6. Quick, A. J.: The Physiology and Pathology of Hemostasis, Philadelphia, Lea & Febiger, 1951.

7. Quick, A. J.; Hussey, C. V., and Stapp, W. F.: The Effect of Heating on the Thromboplastic Activity of Rabbit Brain Extract: A New Test for the Diagnosis of Hemophilia, J. Lab. & Clin. Med. **39**:142, 1952.

8. Quick, A. J.; Pisciotta, A. V., and Hussey, C. V.: Congenital Hypoprothrombinemic States, A. M. A. Arch. Int. Med. **95**:2, 1955.

9. Quick, A. J.: Pediatric Aspects of Hemophilia, Pediatrics **3**:312, 1946.

10. Quick, A. J.: Practical Aspects of Hemophilia, J. Insur. Med. **5**:25, 1950.

11. Brinkhous, K. M.; Langdell, R. D.; Penick, G. D.; Graham, J. B., and Wagner, R. H.: Newer Approaches to the Study of Hemophilia and Hemophiloid States, J. A. M. A. **154**:481, 1954.

12. Langdell, R. D.; Wagner, R. H., and Brinkhous, K. M.: Antihemophilic Factor (AHF) Levels Following Transfusions of Blood, Plasma, and Plasma Fractions, Proc. Exper. Biol. & Med. **88**: 212, 1955.

13. Merskey, C.: Haemophilia Associated with Normal Coagulation Time, Brit. M. J. **1**:906, 1951.

14. Graham, J. B.; McLendon, W. W., and Brinkhous, K. M.: Mild Hemophilia: An Allelic Form of the Disease, Am. J. M. Sc. **225**:46, 1953.

A Roentgenographic Study of Skeletal Lesions in Sarcoidosis

GEORGE N. STEIN, M.D.
HAROLD L. ISRAEL, M.D.
and
MAURICE SONES, M.D., Philadelphia

Sarcoidosis has been recognized in recent years as a generalized disorder of interest and importance to physicians in virtually all branches of medical practice. Roentgenologists have long been familiar with the occurrence of lesions in the bones of the hands and feet of patients with this disease. Estimates as to the frequency of skeletal involvement and as to the clinical value of its demonstration have varied widely. The reported occurrence has ranged from none in one study [1] to 43% in another.[2] The frequency observed in large American series has approximated 20%,* while a recent Scandinavian study of 50 patients demonstrated skeletal lesions in only 6%.[5] It was our impression that the prevalence in patients under our care was lower than that reported in the American studies cited above. It appeared of interest to have a single observer review the roentgenograms of hands and feet which had been routinely secured from the patients who had been referred to our clinics.

A large number of patients with sarcoidosis and others in whom this condition has been suspected are under observation in the clinics of the Henry Phipps Institute and the Graduate Hospital of the University of Pennsylvania. A majority of the patients were referred for study because of chest roentgenograms which suggested mediastinal adenopathy or diffuse pulmonary infiltration, or both. However, the diagnosis in many was suspected because of ocular or cutaneous lesions. It is believed that the patients under observation are representative of those with sarcoidosis in the population of a large American city. Radiographic studies of the hands and feet were available in 175 of these subjects.

Eighty-one of the one hundred seventy-five patients studied were considered to have sarcoidosis on the basis of biopsy evidence of epithelioid tubercles; tuberculosis, histoplasmosis, berylliosis, and other diseases that simulate sarcoidosis were excluded by clinical and laboratory studies. The remaining 94 patients, referred to subsequently as sarcoidosis suspects, comprise those in whom biopsy support of the diagnosis was not obtained, either because the tissue examined was not characteristic of sarcoidosis or because a biopsy specimen could not be secured. It must be presumed that a number of patients in this group had sarcoidosis.

DIAGNOSTIC CRITERIA

Single posteroanterior views of each hand and each foot were available. Roentgenograms were reviewed without prior knowledge of the diagnosis.

Although slight generalized osteoporosis (Fig. 1) has been regarded by some observers as indicative of sarcoid involvement, we have not concurred in this interpreta-

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From the Departments of Radiology and Medicine of the Graduate Hospital and the Sarcoid Clinic of the Henry Phipps Institute of the University of Pennsylvania and from the Woman's Medical College of Pennsylvania.

* References 3 and 4.

Fig. 1.—Roentgenogram of phalanges of third, fourth, and fifth fingers of patient with sarcoidosis, showing slight generalized osteoporosis. This is not regarded as sufficient to warrant a diagnosis of sarcoidosis.

Fig. 2.—Posteroanterior roentgenogram of the phalanges of patient with sarcoidosis, exhibiting stippled appearance of the proximal phalanges of the fourth and fifth fingers as well as sharply demarcated small round radiolucencies in the distal ends of the proximal phalanges of these fingers.

tion, since such changes can be produced by many processes and are not specifically due to sarcoidosis. A moderate degree of osteoporosis or minor disturbances in the trabecular pattern were regarded as suspicious.

Definite diagnoses of sarcoid involvement have been restricted to the following three categories: Single or multiple rounded or oval radiolucencies in the epiphysis surrounded by normal bone, as shown in Figure 2, represent a type of osseous involvement

Fig. 3.—Roentgenogram of phalanges (case reported in text), showing thinning of the cortex, widening of the medulla, and a "honeycombed" trabecular pattern.

often seen in patients with sarcoidosis and referred to as a "punched out" lesion. A second form of bone change is the diffuse type, in which the cortex of the bone is thin and the medullary portion is widened, with a reticular pattern of the trabeculae. This is responsible for a honeycombed or latticework configuration (Fig. 3). The third type is the mutilating one, in which the lesions appear to coalesce to produce destruction of the bone (Fig. 4).

RESULTS

Roentgenograms of the hands and feet of 81 patients with sarcoidosis were studied (Table 1). Sixty-one were regarded as negative; six were thought to be suspicious, and fourteen showed definite osseous lesions. The 94 patients in whom the diagnosis had not been proved had 88 negative roentgen studies; 3 had suspicious lesions, and 3 exhibited definite osseous involvement characteristic of sarcoidosis.

TABLE 1.—*Results of Roentgen Examination of Hands and Feet of 175 Patients Examined in the Sarcoid Clinic*

	Patients, No.			
	Total	Definite Osseous Lesions	Suspected Involvement	Negative
Sarcoidosis	81	14 (17.2)*	6 (7.4)	61 (75.4)
Sarcoidosis suspects	94	3 (3.1)	3 (3.1)	88 (93.8)

* Percentages are given in parentheses.

TABLE 2.—*Sites of Osseous Lesions in Fourteen Patients with Sarcoidosis*

Bones Involved	No. of Times Involved
Upper Extremities	
Phalanges	8
Metacarpals	1
Carpals	5
Radius	1
Ulna	1
Lower Extremities	
Phalanges	2
Metatarsals	2
Tarsals	1
Tibia	1

Lesions were present in both hands and feet of two patients with sarcoidosis. The bones of the hands alone were involved in nine patients, and in three subjects the bones of the feet showed changes due to sarcoidosis without evidence of osseous lesions in the hands. Osseous lesions in the tarsal and carpal bones have been rarely reported; yet in this series six instances of involvement of these bones were encountered (Table 2).

An attempt was made to correlate the type and severity of pulmonary involvement and the presence of cutaneous sarcoid lesions with the occurrence of osseous changes. No relationship was evident.

It is generally considered that the small bones of the hands and feet are most frequently involved in sarcoidosis; reports describing involvement of other bones are few.† In order to determine whether or not disseminated involvement is commoner than has been thought, it appeared desirable to make complete bone surveys of a number of patients. Bone surveys were carried out in 10 patients with sarcoidosis who had demonstrable involvement of the bones of the hands or feet, with the belief that these subjects would be most likely to show other areas of involvement. The survey consisted of lateral roentgenograms of the skull and entire spine and anteroposterior views of both upper and lower extremities and the pelvis. In addition, an anteroposterior roentgenogram was made of the abdomen in an effort to detect opaque renal calculi. No

Fig. 4.—Roentgenogram showing destruction of the tip of the terminal phalanx of the fourth finger of patient with sarcoidosis. Note the changes in the proximal and middle phalanges of the third and fourth fingers.

† References 4, 6, and 7.

further skeletal lesions were detected by the survey. Roentgenologically demonstrable lesions were confined to the hands or feet of nine patients. Involvement of the hands, feet, radius, ulna, and tibia had previously been recognized in a patient whose history is detailed below; the survey disclosed no additional lesions in this case. It seems reasonable to conclude that the roentgenographically demonstrable osseous lesions of sarcoidosis are as a rule restricted to the hands and feet.

Sarcoidosis of the bones of the hands and feet is usually an incidental finding. However, attention should be directed to the occasional instance in which osseous involvement is a dominant feature of the disease, as it was in the following case.

A Negro woman was first seen in 1941, at the age of 21, during her second pregnancy. Lesions had developed on the skin of her back, chest, face, and legs. Shortly after delivery arthralgia was noted. Roentgen examination of the chest revealed an enlarged mediastinal shadow; films of the hands and feet were negative. A lymph node biopsy at this time was interpreted as consistent with sarcoidosis.

She was fairly well until 1946, when she noted swelling and deformity of the fingers associated with pain and stiffness. Between 1947 and 1950 she attended a number of clinics without obtaining relief.

She was seen at the Medical Clinic of Graduate Hospital in 1950 because of arthritic symptoms. At this time, the fingers of both hands were swollen and deformed. A few shiny nodules were present on the arms and thighs. There were no palpable lymph nodes. X-ray examination of the bones showed extensive involvement of all of the small bones of the hands and feet as well as the proximal end of the tibia and the distal ends of the radius and ulna (Fig. 5*A* and *B*). Results of examination of an excised skin nodule were reported as consistent with sarcoidosis.

In October, 1950, she received 3 gm. of cortisone over a period of three weeks, with improvement in the pain, swelling, and mobility of the joints.

When last seen, in September, 1955, she felt fairly well. There was less swelling of the joints and increased mobility. X-rays of the hands and feet showed considerable improvement.

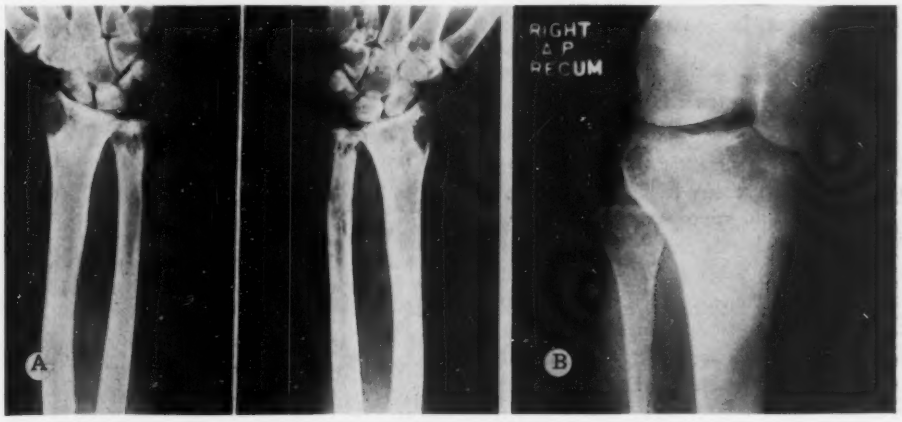

Fig. 5.—*A*, roentgenograms of both wrists, exhibiting lesions of sarcoidosis involving the radius and ulna bilaterally (case reported in text). *B*, Anteroposterior projection of knee, showing rounded radiolucent lesion of sarcoidosis involving the proximal end of the tibia (same patient).

COMMENT

Contrary to expectation, a high prevalence (17.2%) of skeletal lesions in the hands and feet of patients with sarcoidosis was found.

Osseous involvement in sarcoidosis is rarely responsible for symptoms. The lesions are important to the physician, however, for their demonstration by roentgenograms provides useful evidence to support the diagnosis of sarcoidosis. Osseous lesions of this type are rare in tuberculosis, histoplasmosis, and berylliosis, the diseases which commonly produce histologic and clinical changes similar to those of sarcoidosis. For

this reason, the demonstration of lesions in the hands or feet represents a significant addition to the corroborative clinical evidence, which is as important as histologic evidence for the diagnosis of sarcoidosis. It should be emphasized that histologic demonstration of epithelioid tubercles is a requisite for diagnosis and that characteristic roentgenographic changes are not by themselves sufficient to establish the presence of sarcoidosis.

The frequency with which involvement of the hands and feet was roentgenologically demonstrable in this series is sufficiently high to warrant the recommendation that roentgenographic examination of these bones be a routine procedure in the study of patients in whom sarcoidosis is suspected.

SUMMARY

Roentgenographic study of the hands and feet of 81 patients with sarcoidosis showed characteristic osseous lesions in 17.2%.

Complete bone surveys of 10 patients with lesions of the hands and feet indicated that involvement of other bones is infrequent.

Osseous involvement by sarcoidosis is usually asymptomatic, but an instance is reported of a patient in whom extensive mutilating changes clinically simulated advanced arthritis.

Roentgenographic demonstration of lesions in the bones of hands and feet provides valuable corroborative evidence for the diagnosis of sarcoidosis. Roentgenographic study of these bones should be a part of the examination of all patients in whom sarcoidosis is suspected.

REFERENCES

1. Ackerman, A. J.: Roentgenological Aspect of Sarcoidosis, Am. J. Roentgenol. **59**:318, 1948.

2. Gottlieb, M. E.: Om Knogleforandringer ved lymfogranulomatosis benigna, Nord. med. **29**:57, 1946.

3. Holt, J. F., and Owens, W. I.: Osseous Lesions of Sarcoidosis, Radiology **53**:11, 1949.

4. Longcope, W. T., and Freiman, D. G.: Study of Sarcoidosis Based on Combined Investigation of 100 Cases Including 30 Autopsies from Johns Hopkins Hospital and Massachusetts General Hospital, Medicine **31**:1, 1952.

5. Nitter, L.: Changes in the Chest Roentgenogram in Boeck's Sarcoid of the Lungs, Acta radiol., Supp. 105, p. 1, 1953.

6. Robert, F.: Les Manifestations osseuse de la maladie de Besnier-Boeck-Schaumann (la maladie de Perthes-Jüngling), Semaine hôp. Paris **25**:2327, 1944.

7. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): A Study of 35 Cases, Am. Rev. Tuberc. **49**:299, 1944.

Idiopathic Paroxysmal Myoglobinuria

Report of Two Cases and Evaluation of the Syndrome

LEOPOLD REINER, M.D.
NADYA KONIKOFF, M.D., New York
MARK D. ALTSCHULE, M.D.
GUSTAVE J. DAMMIN, M.D.
and
JOHN P. MERRILL, M.D., Boston

Idiopathic paroxysmal myoglobinuria is a rare disorder. Adams, Denny-Brown, and Pearson [1] in their comprehensive treatise, "Diseases of Muscle," state that they have never seen a case. A search of the literature reveals reports of fewer than two dozen cases, to which we add observations on two others.

REPORT OF CASES

CASE 1.—A 46-year-old white man of Irish descent was admitted to Beth Israel Hospital in July, 1948, soon after he had suddenly become incapacitated by intolerably painful cramps in his thighs; these had come on without warning when he had attempted to crawl under a fence after climbing a steep hill. He had found himself unable to rise or to straighten himself from the stooped position but had been able to sit with his legs extended. He had perspired profusely during this episode.

Ever since childhood the patient had experienced weakness and pains in the muscles of arms and legs when active. The occurrence of these symptoms had been unpredictable and had had no constant relation to type or degree of muscle use. He had been unable to participate in any competitive sports during his youth. He had never observed any abnormal coloration of the urine.

The patient had had hypertension for several years. Two years previously he had been hospitalized for left hemiplegia; at that time his systolic blood pressure was 240 to 260. He was subsequently advised to take a salt-poor diet.

The patient was one of four siblings; none of the others had suffered from muscular pain or weakness. There were no known neurological or muscular disorders in the family. His parents had had hypertension, and his father had died in his 70's of a cerebrovascular accident. The patient was married and had four normal children.

Physical examination on admission revealed a well-developed and well-nourished man. The temperature was 98.6 F; respirations were 24 per minute, and the blood pressure was 208/138. The heart was enlarged to percussion. There was marked spasm of the anterolateral thigh muscles, more pronounced on the right. The legs were held in extension. Active leg-raising was limited to 20 to 30 degrees because of pain; patellar reflexes could not be tested, because the patient would not flex his knees. There were slight left facial weakness, hyperreflexia of the left arm, and reinforcement contraction of the left hand, all residuals of the cerebrovascular accident two years before.

The first urine passed after admission was wine-red in color and acid in reaction. Its specific gravity was 1.013; the guaiac test was 4+, and the protein test was 3+. The sediment contained coarsely granular casts and 8 to 10 erythrocytes per high-power field. The blood plasma was of normal color; the blood hemoglobin concentration was 19.2 gm. per 100 ml. The red blood cell count was 6,890,000; the white blood cell count was 16,150, of which 95% were leucocytes. The blood nonprotein nitrogen concentration was 57 mg. per 100 cc. on the day after admission.

The pain in the thigh muscles, which remained severe during the next few days, soon became restricted to the right quadriceps femoris muscle. All pain and limitation of motion disappeared by the seventh hospital day. The color of the urine changed from red to brown and reverted to normal straw color after three days, by which time also red blood cells had disappeared from the urine sediment. On the fourth day oliguria developed and the blood nonprotein nitrogen level began to

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From the Medical Services and Pathology Laboratories, Beth Israel Hospital and Peter Bent Brigham Hospital, and the Departments of Pathology and Medicine, Harvard Medical School. Present address: The Bronx Hospital (57) (Dr. Reiner).

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Fig. 1 (Case 1).—Muscle biopsy specimen showing segmental necrosis of uniform hyaline or sinuous (center of photograph) appearance. There are fibers whose contents are fragmented in association with the presence of intrasarcolemmal macrophages. There is no exudative reaction in the interstitium. (Figs. 1 to 7 are from the biopsy of the first myoglobinuric episode.) Eosin and methylene blue; × 90. (Figs. 1 to 5, inclusive, are from tissues fixed in acetic acid-Zenker's fluid.)

rise; within another two or three days the latter had risen to 115 mg. per 100 cc. Facial edema developed.

Peritoneal lavage by means of sump drains was commenced on the seventh day. Urinary output during this procedure varied between 90 and 200 cc. per 24 hours; the urine was yellow, with a specific gravity of 1.013 to 1.014, and the test for protein

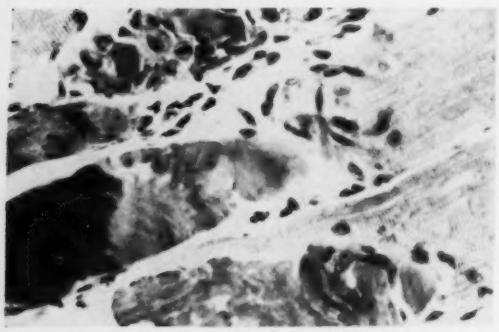

Fig. 2 (Case 1).—Hyaline necrosis of muscle fibers, illustrating both the uniform and the sinuous appearance. Demarcation of the necrotic segments from the unaffected parts of the fibers by spindle cells of mesenchymal origin. The upper fiber is being fragmented by the intervention of macrophages. Eosin and methylene blue; × 180.

Fig. 3 (Case 1).—Segmental necrosis of muscle fibers which are partly achromic and partly deeply stained with eosin. A faint pattern of longitudinal striation is recognizable in the achromic portion of the fiber. No proliferation of sarcolemmal nuclei or invasion of the sarcolemmal tube by mesenchymal cells. Eosin and methylene blue; × 180.

was consistently 3+ to 4+. The sediment contained many red blood cells, 3 to 10 white blood cells, and some coarsely granular casts per high-power field. Peritoneal lavage was discontinued after 96 hours because of signs of peritonitis; however, the urinary output began to rise shortly thereafter, reaching 2600 cc. per 24 hours one week later. The maximum specific gravity was 1.015. Coarsely granular casts persisted in small numbers in the sediment. Nitrogen retention (up to 146 mg. per 100 cc., of nonprotein nitrogen) lasted for another 13 days. The patient was discharged 41 days after admission, with a nonprotein nitrogen concentration of 60 mg. per 100 cc. of blood and some residual muscle weakness of the thighs. A muscle biopsy was taken from the right thigh on the seventh day of illness (at the time of onset of peritoneal dialysis).

During the ensuing five years the specific gravity of random urine samples ranged from 1.002 to 1.022. Occasionally there was slight albuminuria, but all the urine specimens were free of formed elements. The patient was able to do full-time sedentary work as a mail clerk, but weakness necessitated the use of a cane for walking. The muscles of the thighs and upper arms were flabby and of small girth, as they had been since his early youth. He could not rise from the horizontal position without the help of his arms. The strength of his hands was unimpaired.

The patient returned in October, 1953, because of an episode of severe muscle pain and pigmentation of the urine 10 days previously. Without prodromal symptoms of any kind, he had experienced severe pain in the left thigh on getting out of a warm tub bath. The pain had been relieved somewhat by placing the leg in extension. Three hours later the urine had been "like blood." Subsequent urines, the patient took care to note, had been of normal color. Pain had persisted for two days and had been followed by muscular stiffness and discomfort for another two days. A muscle biopsy was taken from the anterior left thigh 6 days later, i. e., 10 days after the onset of the attack. At that time, the urine had a specific gravity of 1.006; there was no albuminuria, and no casts or red blood cells were seen.

Microscopical examination of the muscle biopsy specimen taken on the eighth day of the first episode showed marked and widespread damage to the contractile elements. The change was distinctly segmental and, as judged from composite views of longitudinal and transverse sections, involved not only every fiber somewhere in its length but also each one in several places. In sections stained with eosin and methylene blue, after fixation in acetic acid-Zenker's fluid, the continuity of the fibers was found to be interrupted by various-

sized segments of hyaline necrosis (Fig. 1). Although usually homogeneous in appearance, the hyaline change occasionally took the form of sinuous bands of alternating density (Fig. 2).

A second type of segmental necrosis seen less frequently manifested itself in fibers which failed to take any stain and appeared achromic (Fig. 3). In such fibers there was loss of the normal transverse striation but occasional persistence of faint longitudinal fibrillarity. Small patches of normal color and of normal striation were occasionally observed within the decolorized segments. Combinations of hyaline and achromic necrosis were observed (Fig. 4).

For the most part the necrosis involved the entire thickness of the fiber, but occasionally only a portion of the thickness was involved. The transition from the normal to the necrotic portion was either gradual or abrupt. Often the damaged segment was sequestrated from the rest of the fiber by a gap which was filled with an amorphous protein precipitate (Fig. 5; cf. Fig. 10).

In sections fixed in formalin and stained with hematoxylin and eosin the necrotic fibers appeared granular and basophilic rather than hyaline and acidophilic. This was due to encrustation with granular calcium phosphate, which was identified by its positive reactions with alizarin and with von Kossa's silver stain (Fig. 6). This mineral deposit was absent from sections fixed in acetic acid-Zenker's fluid, the calcium having been dissolved by the acid.

Two other forms of degeneration, both infrequent, also were encountered. One consisted of coarse vacuolization of the fiber with little change in its normal striation (cf. Fig. 11); the other, found only in association with fiber achromia, was a granular disintegration of the sarcomeres that resulted in the formation of parallel rows of bead-like structures.

Phagocytic cells appeared within the necrotic hyaline fibers, which thereby became fragmented into progressively smaller masses having angular contours (Figs. 1 and 2; cf. Fig. 9). This phenomenon was irregular in distribution and degree. No phagocytic reaction was found in the achromic fibers.

Proliferation of sarcolemmal nuclei was occasionally seen in both the normal and the diseased muscle fibers. Multinuclear muscle buds and regeneration by cellular bands was present but rare (Fig. 7). There was no exudative cellular reaction except for rare foci of perivascular lymphocytes in the perimysium. The endomysium contained a few inconspicuous collections of histiocytes. There was no hemorrhage, recent or remote.

Neither the necrosis nor the reparative process appeared to be uniform in different fibers or even

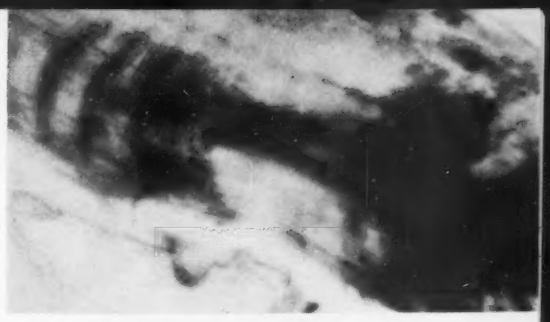

Fig. 4 (Case 1).—High-power view of necrotic fiber segment combining hyaline necrosis, achromic necrosis, and small patches of preserved fiber substance. The transition between the various components is gradual. The sarcolemmal sheath is preserved. Eosin and methylene blue; × 513.

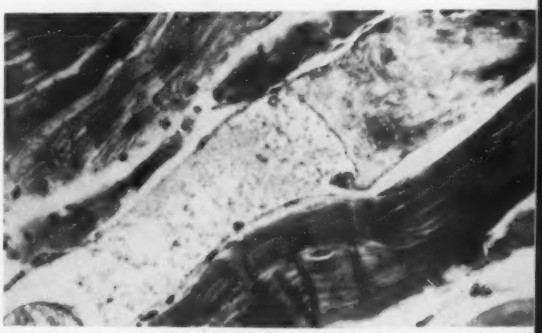

Fig. 5 (Case 1).—Necrotic fiber showing retraction of sarcoplasm. Note the granular protein precipitate in the sarcolemmal tube. Eosin and methylene blue; × 180.

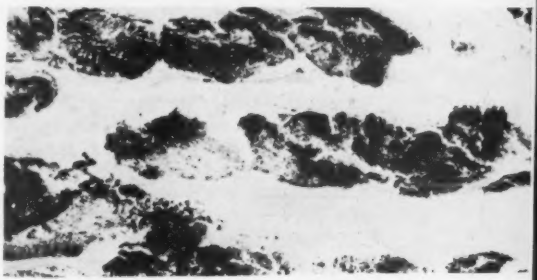

Fig. 6 (Case 1).—Formalin-fixed tissue. The black granules which outline the necrotic muscle segments are calcium phosphate. Two normal, non-mineralized fibers are faintly outlined on top and in right lower field of this photograph. Von Kossa stain; × 90.

Fig. 7 (Case 1).—Fragmentation of necrotic muscle. Mineral precipitate in a hyaline fiber. There are two examples of muscle regeneration. Formalin fixation. Hematoxylin and eosin; × 180.

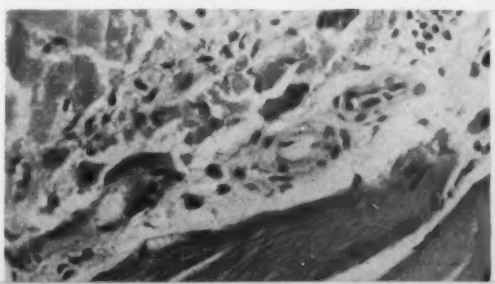

Fig. 8 (Case 1).—Biopsy of skeletal muscle obtained during the second myoglobinuria episode. The muscle fibers in the photomicrograph are normal. There are several multinucleated muscle giant cells. Formalin fixation. Hematoxylin and eosin; × 140.

in different segments of the same fiber (Fig. 1; cf. Fig. 11).

In the biopsy specimen taken on the 10th day of the second attack only a very few fibers were found damaged by segmental hyaline necrosis. Unlike the findings in the first biopsy, neither sinuous hyaline bands, achromia, nor calcification of necrotic segments were observed. The segments of hyaline necrosis were continuous with the intact fiber portions. There was no exudative reaction aside from a loose accumulation of lymphocytes about an occasional damaged fiber. A moderate number of multinucleated giant cells was seen. Their distribution was topographically unrelated to the acute process; they were sometimes adjacent to perfectly normal muscle fibers and were sometimes distributed as isolated units in the interstitium (Fig. 8). Their cytoplasm was eosinophilic and was not definitely striated.

In both biopsy specimens the diameters of the muscle fibers were within normal range. The interstitium neither was increased nor showed adipose transformation.

Fig. 9 (Case 2).—Segmental necrosis of muscle sarcoplasm and fragmentation by intrasarcolemmal macrophages. There is some proliferation of sarcolemmal nuclei in the normal fibers. A normal arteriole is at the lower border of the photograph. The interstitial hemorrhage is incidental to the trauma of the biopsy. Modified Bouin's fixative. Hematoxylin and eosin; × 75.

CASE 2.—A 42-year-old white man was admitted to the Peter Bent Brigham Hospital for the first time in December, 1954, because of anuria. Two weeks before admission, while on a hunting trip, he had had a syncopal attack associated with tonic muscular contractions. Upon regaining consciousness after lying on the frozen ground for half an hour, he had noted soreness of the muscles and dark-red urine. He had been nauseated and had vomited. The urinary volume had subsequently become greatly reduced. He had remained at home for one week, but because of persistent muscle soreness, nausea, and weakness he had been admitted to a local hospital. There the blood urea nitrogen level had been 41 mg. per 100 cc.; the erythrocyte sedimentation rate, 34 mm. in an hour (normal, 0-10 mm. in an hour), and the serum potassium concentration, 7.6 mEq/liter (normal, 3.5-4.5 mEq/liter). Muscle twitching and edema of the ankles, feet, hands, and periorbital tissues were recorded.

Because of anuria he had been transferred to the Peter Bent Brigham Hospital, where the following history was obtained: Twenty-three years ago, at the age of 19, after playing basketball, the patient lost consciousness and upon recovery exhibited tightness of the muscles, weakness, confusion, and disorientation. The urine had a dark-mahogany color for two days. A similar episode occurred in the same year; a third, in 1950, and a fourth, in 1951. The present attack was thus the fifth paroxysm. All but one of these were preceded by unusual exertion, and in each attack the urine became dark brown. During the past three years he has had episodes consisting only of dizziness, faintness, scotomata, extension of the arms, and tongue biting. These episodes did not follow exertion, and the urine did not darken afterwards. There was no history of injury or asphyxia at birth and no history of head trauma in later life.

Studies conducted elsewhere after the fourth major episode in 1951 showed a flat glucose-tolerance curve. Cerebrospinal fluid obtained by lumbar puncture was normal. Electroencephalograms were suggestive but not diagnostic of epilepsy. Epilepsy, chronic nephritis, and hypoglycemia were the diagnoses made.

There was no family history of epilepsy. The patient had three children who were all in good health.

On physical examination at this hospital the temperature was 97 F; the pulse rate, 74 per minute; the respiratory rate, 24 per minute, and the blood pressure, 170/100 mm. Hg. The patient appeared well nourished and well developed. He was slow in speech and complained of nausea, chilliness, and pain in the muscles of the extremities.

The pertinent findings were slight icterus, tenderness of the muscles of the legs and upper arms, edema of the extremities and periorbital tissues, and moderate obtundity. The ocular fundi were normal.

The laboratory studies included a negative serologic test for syphilis and a negative Coombs test. No cold agglutinins were demonstrated. There was no occult blood in the feces. A skin test for tuberculin sensitivity with first-strength PPD was negative. The patient's blood group was B, Rh-positive. The urine was straw-colored and had a specific gravity of from 1.003 to 1.008. Its pH was 5.5; there was 1+ to 2+ proteinuria; the sediment initially contained erythrocytes, leucocytes, and hyaline and finely and coarsely granular casts but was normal later. The initial leucocyte count was 12,750, with 92% neutrophilic polymorphonuclear cells; later counts were normal. The initial blood urea nitrogen concentration was 222 mg. per 100 cc.; on discharge three weeks later it was 110 mg. On admission the fasting blood sugar concentration was 98 mg. per 100 ml.; the carbon dioxide content, 15.3 mM/liter; the chloride concentration, 90 mEq/liter; the sodium level, 140 mEq/liter; the calcium concentration, 4.8 mM/liter, and the phosphorus concentration, 4.7 mM/liter. The initial electrocardiogram showed potassium intoxication, but later tracings gradually returned to normal. Roentgenograms of the chest and abdomen showed no abnormalities. An electroencephalogram showed moderate slowing with occasional precentral spikes. The prothrombin percentage, originally 30% of normal, rose to 70%. There was a gradual fall in the hematocrit value from 40% to 27%.

The patient was afebrile throughout a three weeks' course in the hospital. The blood pressure initially varied between 216/96 and 190/110. At the time of discharge readings of 112/66 and 140/78 were obtained. Urinary output was much diminished at first (480 ml. per 24 hours) but gradually returned to normal. The body weight fell from 84 to 73.2 kg. The patient was given diphenylhydantoin (Dilantin), chlorpromazine (Thorazine), and testosterone. There was gradual clinical improvement, and in a few days the patient was no longer obtunded. Nausea, vomiting, and muscle pain in the extremities disappeared. There was no postural hypotension. A roughening of the skin was interpreted as keratosis pilaris.

Fig. 10 (Case 2).—Segmental necrosis of muscle fibers with retraction of sarcoplasm. Note the proteinaceous fluid filling the sarcolemmal tube between the retracted necrotic fiber segments. Modified Bouin's fixative. Hematoxylin and eosin; × 75.

Biopsy of the gastrocnemius muscle on the 20th day after the onset of this episode showed segmental sarcoplasmic degeneration, proliferation of sarcolemmal cells, and scant infiltration with mononucleated and multinucleated macrophages (Figs. 9, 10, and 11), changes identical with those seen in Case 1. The muscle biopsy was interpreted as compatible with idiopathic paroxysmal myoglobinuria. Discharge diagnoses were primary skeletal myopathy with myoglobinuria, acute renal failure, and epilepsy.

The patient was admitted for further study in March, 1955, three months later. His convalescence had been uneventful, and he had returned to full-time work in his former position with a collection agency. There had been no recurrence of symptoms, but he was unable to walk any long distance without developing cramps in the legs.

No pertinent abnormalities were observed on physical examination. There was no muscle tenderness, weakness, or wasting. The blood pressure was 120/80. Keratosis pilaris was still present. The urine was of normal color and had a specific gravity of 1.007 to 1.010 and a normal sediment. Hematologic studies were unremarkable; the hematocrit value was 42%. The blood urea nitrogen level was 23 mg. per 100 ml. The six-hour glucose-tolerance test was normal, and an electrocardiogram also was normal. The phenolsulfonphthalein excretion was 55% in two hours. An electroencephalogram was considered slightly abnormal in that there were infrequent low-voltage precentral

Fig. 11 (Case 2).—In addition to necrotic fibers and fragmentation with intrasarcolemmal macrophages, the field shows achromia of a muscle fiber with residual longitudinal striation. Adjacent is a non-necrotic fiber segment showing vacuolization. Modified Bouin's fixative. Hematoxylin and eosin; × 75.

spikes. A muscle biopsy at this time showed minimal focal alterations qualitatively similar to those observed in the first biopsy.

The patient was discharged with instructions to avoid strenuous exercise. Diphenylhydantoin was prescribed.

COMMENT

This comment is based on 21 cases reported in the literature * and on the 2 cases reported here.† These 23 cases have in common a history of paroxysmal paralytic myoglobinuria of obscure (i. e., idiopathic) etiology, but the group is perhaps not homogeneous in other respects.‡

There were 17 male and 4 female patients.§ At first examination seven ‖ were 14 years of age or less, the youngest [3] being 2 3/12 years old. Several adult patients had histories of muscle weakness and pain since childhood or early youth, although myoglobinuria was often not observed until some time later. One patient, in addition to having muscle weakness, had suffered from a myotonic muscle reaction in his hands.[9] In the majority of patients the myoglobinuric attacks were repetitive, although in most cases they occurred no more than once or twice a year. There were exceptions, however: One patient estimated at 50 the number of attacks experienced over a period of seven years,[19] and another one not otherwise included in this survey experienced as many as 5 or 6 attacks in a single year.[10]

A familial incidence of the disease was established in two sibships ¶ and suspected in one.[16] In Hed's [7] family three out of five brothers were affected; Hittmair [10] described the disease in a sister and one brother among a sibship of six.

Characteristics of the Myoglobinuric Episode

The attacks began acutely with muscle pain as the leading symptom in the majority of cases. There were associated symptoms, such as chills, anorexia, vomiting, epistaxis, melena, pallor, sweats, anxiety, tachycardia, and abdominal pain. In several instances the body temperature was above 37.5 C during the attacks. The white blood cell count was elevated above 10,000 cu. mm. in about a third of the patients for whom data were given. Upper respiratory infections preceded the myoglobinuric attacks in the 4½-year-old child reported by Buchanan and Steiner [3] and also the paroxysm of a 9-year-old boy who subsequently developed pneumonia (Schaar [17]). The 15½-year-old girl observed by Stokes # complained of sore throat and headache for two days before the onset of her first (and fatal) attack of myoglobinuria.

Although the attacks were precipitated by physical exercise in about half the patients, the severity of the attacks was not always closely correlated with the intensity or the type of bodily exercise; this was true even in different attacks in the same person. Exercise in susceptible persons was not necessarily followed by an attack; several patients continued actively in competitive games.* On the other hand, one man could precipitate myoglobinuric episodes at will merely by straining his thigh muscles.[12] One boy,[20] aged 6½, experienced the initial attack while taking his first out-of-door walk after prolonged confinement for chicken pox. To Wissler [20] this situation was reminiscent of a disease of horses known as "monday morning sickness" (summer disease, Kreuzschlag, Harnwinde, maladie de Lucet), i. e., muscular paralysis and myoglobinuria of abrupt onset and often fatal outcome upon resumption of activities after prolonged stable rest. The opposite, however, apparently occurred in the patient reported by Spaeth [19]; here prolonged rest increased the tolerance to subsequent exercise. A few patients developed

* References 2-20.

† Because of insufficient data three additional cases of the disorder (Hittmair,[10] Millikan,[21] and Stokes [cited by Acheson and McAlpine [2]]) are not considered in this review except where specifically mentioned.

‡ References 6 and 23.

§ References 5, 6, 10, and 15.

‖ References 3, 5, 11, 13, 14, 17, and 20.

¶ References 7 and 10.

Cited by Acheson and McAlpine.[2]

* References 2 and 8.

some of their attacks during sleep (Hed,[8] Case 2; Meyer-Betz [14]).

The case of Wissler [20] suggests (cf. Hipp [9]) that excessive walking may, in susceptible persons, precipitate paroxysms of myoglobinuria that might be misinterpreted as march hemoglobinuria. This is illustrated by Case 2 of Fleming and Kinsman,[22] a 23-year-old man who since the age of 16 had had repeated attacks of urinary discoloration after excessive walking. Although this case was reported as an example of march hemoglobinuria, the prominence of associated pain and weakness in the muscles of the lower extremities suggests that the patient actually suffered from idiopathic paroxysmal myoglobinuria.

The muscle pains, often severe and sometimes prostrating, involved the calves and frequently ascended to the thighs and the back. Several patients also had involvement of the arms. Occasionally pain (and weakness) became generalized. The affected muscles were tender, hard, and contracted ("woody," "in spasm"). Pes equinus, nearly always bilateral, was mentioned in about a third of the reported cases. The pains usually disappeared within a matter of days, although occasionally they lasted for a week or more.

Muscular weakness or outright paralysis was the next most outstanding manifestation and was seemingly due to organic muscle damage. In two articles † muscle weakness was reported without specific mention of coexisting muscle pain. Motor impairment, like the pain, affected the legs constantly. Walking was difficult or impossible; sometimes motor impairment was so widespread that the patients were too weak to sit up in bed, to raise their heads, or to feed themselves. Weakness either disappeared within 24 hours or persisted for days or weeks, roughly in correlation with the over-all severity of the attacks. Deep tendon reflexes in the afflicted extremities were commonly weak or absent during the attack and in convalescence. Involvement of repiratory and deglutitional muscles occasionally caused pseudobulbar paresis; although this was as a rule transitory, one patient apparently died of this complication.[3]

Electrical stimulation of nerves gave results indicative of a primary muscular disorder.‡ Wissler,[20] however, observed marked mechanical irritability of the facial, ulnar, and radial nerves one hour after the onset of the attack. His patient had minimal trismus; the muscles of the upper extremities apparently were uninvolved.

Except for pain, sensory disturbances were usually absent. One patient, however, had paresthesias of the feet and numbness of the hands.[10] Another had hypalgesia and hypesthesia of the peripheral parts of all four limbs coincidentally with nearly complete quadriplegia.[3]

Several patients showed muscle wasting. Kreutzer's patient,[12] a 39-year-old man who had had recurrent attacks since childhood, showed slight wasting in the proximal muscle groups of both the upper and lower extremities. The contrastingly large size of the calves caused an appearance suggestive of progressive muscular dystrophy. Scherwin's patient,[18] a 38-year-old man who gave a history of recurrent myoglobinuric attacks covering only a few years, showed atrophy not only of the shoulder and pelvic girdles but also the quadriceps femoris and triceps surae; he had grown so weak that he could barely walk and was unable to dress or wash himself. Wissler's patient [20] developed "unequivocal signs of pseudohypertrophic muscular atrophy" § after his first myoglobinuric attack, at the age of 6½. The 13-year-old boy reported by Meyer-Betz [14] exhibited retardation of growth and poor muscular development after suffering a number of attacks; while recovering from a particularly severe attack the patient raised himself from a lying position in the fashion of a patient with muscular dystrophy, but Meyer-Betz dismissed that diagnosis. The 30-year-old man

† References 3 and 14.

‡ References 10 and 14.

§ Wissler, H.: Personal communication to Acheson and McAlpine.[2]

reported by Acheson and McAlpine [2] had had repeated myoglobinuric attacks for seven or eight years; he showed minor wasting of the neck and shoulder muscles and more definite atrophy of the upper arms. His pelvis and thighs appeared to be of normal girth, but his calves seemed hypertrophied. He too raised himself from a squatting or lying position in the fashion of a patient with muscular dystrophy. Our first patient showed flabbiness, weakness, and diminished girth of both arms and thighs, all present but not progressive since adolescence. He likewise was unable to rise from a lying position without the help of his arms and hands. The calves were not unduly prominent. Hittmair's patient,[10] a 42-year-old woman, displayed asymmetrical atrophy in arms and legs after her fourth attack.

The histories of two subjects suggested a relation between the occurrence of convulsive seizures and the development of myoglobinuric attacks: The subject of Case 2 of the present report had several of his attacks in association with epileptic seizures, and the patient of Hipp and Shukers [9] had his first myoglobinuria episode immediately after electroshock treatment that was administered for an emotional depression. That severe convulsive seizures, spontaneous or induced, represent the most strenuous type of muscular contractions possible is attested by the associated occurrence of fractures, dislocations, and muscle ruptures. Physiologic studies also show that the cardiovascular [24] and metabolic [25] changes that occur in such seizures may be far greater than those observed after any type of voluntary exertion.

Several authors || have placed emphasis on the occurrence of nonmyoglobinuric muscular dystrophy in blood relatives of several of the myoglobinuric patients mentioned in this survey. Three maternal uncles of the 6-year-old boy described by Wissler [20] showed muscle wasting. Louw and Nielsen [18] established the occurrence of muscular dystrophy over three generations in eight members of the maternal ancestry of a 10-year-old boy who himself suffered from paroxysmal myoglobinuria. Because only males were affected, these authors suggested that the disease complex was transmitted as a sex-linked recessive character. A sister of the 30-year-old man with paroxysmal myoglobinuria described by Acheson and McAlpine [2] had pseudohypertrophic muscular dystrophy. Every one of the three myoglobinuric patients just mentioned displayed muscular dystrophy either when first seen or at some time during the follow-up period. Although the subject of Case 1 of the present study exhibited wasting of the shoulder and thigh muscles, we could not elicit any familial history of muscular disorders.

The case of Günther,[27] frequently cited as an example of idiopathic myoglobinuria, has been omitted from this review. The patient, a 54-year-old man who died after two months of illness, presented a clinical course which differed greatly from the usual picture. There were marked edema of the extremities and paralysis of the muscles, and myoglobinuria was intermittent over a period of about five weeks. There had been no similar episode previously. It is possible that the patient actually had dermatomyositis, as suggested by Elek and Anderson.[6] These last authors also submit, on clinical grounds, that the cases of Paul [15] and Scherwin,[18] which we included in the present survey, may likewise have been examples of dermatomyositis rather than of idiopathic paroxysmal myoglobinuria.

Several muscle disorders other than idiopathic paroxysmal myoglobinuria cause excretion of muscle pigment in the urine ¶—as, for instance, Haff disease, which occurs in small epidemics along the Baltic coast of East Prussia and about inland lakes in Sweden.[28] After the ingestion of large amounts of fish the victims of this disease abruptly experience excruciating muscle pain, with limitation of the motion, exquisite muscle tenderness, and passage of dark urine. An individual susceptibility seems to predispose to the disease. Myoglobinuria also follows

|| References 2 and 23.

¶ References 1 and 23.

crushing injuries to skeletal muscle, high-voltage accidents, and carbon-monoxide poisoning. It is occasionally observed as a complication of the anterior tibial syndrome and possibly occurs also with dermatomyositis.# As in idiopathic myoglobinuria, any of the above-mentioned diseases may terminate in death from renal failure due to acute tubular necrosis ("lower nephron nephrosis," "myoglobinuric nephrosis").

Renal Involvement and Its Manifestations

In the cases reviewed in this article, discoloration of the urine ("red," "wine-colored," "like dark beer") followed the muscle pain, usually within 12 to 24 hours; it was, however, observed as early as 90 minutes after the onset of pain. In one exceptional case [10] its appearance was delayed for from two to five days in four different attacks. The urinary discoloration disappeared within a day or two in the majority of episodes. It persisted for from two to eight days in severer attacks. Three patients who died on the 7th, 9th, and 15th days, respectively, had myoglobinuria for the first 4, 3, and 7 days, in order.* In Cases 1 and 2 of the present report gross myoglobinuria lasted for three and two days, respectively.

The pigment responsible for the urinary discoloration was identified spectroscopically as myoglobin for the first time in 1944 by Louw and Nielsen.[13] This finding has been confirmed in 12 subsequent instances of the disease.† Because of the closeness of the absorption bands of muscle and blood hemoglobin, earlier authors had misinterpreted the urinary pigment as oxyhemoglobin and methemoglobin.

Myoglobin renders urine benzidine-positive. A bloody color of the urine with no erythrocytes in the urinary sediment is as characteristic of myoglobinuria as it is of hemoglobinuria. As in the two cases of this report, it is, of course, possible for erythrocytes to appear in the urine during an attack of paroxysmal myoglobinuria; this may be a manifestation of the complicating acute tubular necrosis ("lower nephron nephrosis," "myoglobinuric nephrosis"). Bywaters and Dible [4] considered the possibility that the erythrocytes reportedly found in the urine of their patient who had died of acute tubular necrosis might actually have been pigment granules of myoglobin. Albuminuria accompanied myoglobinuria; hyaline and granular casts were sometimes found even in mild attacks.

Data from cases reviewed support the present-day concept that tubular necrosis and renal insufficiency are not primarily due to myoglobin. In terms of number of patients, acute renal failure is quite uncommon. However, when such failure does supervene, shock (Case 1; Meyer-Betz [14]), intolerable muscle pain (Case 1), and exposure to cold (Case 2) have been present and probably constituted the major causative factors. In one patient [19] acute renal failure ensued when a myoglobinuric episode was induced by exercise following administration of cortisone. Nonetheless, the great frequency with which transient proteinuria and cylindruria accompanied individual attacks of proxysmal myoglobinuria without renal failure may represent a minor degree of renal injury produced by myoglobin as such.

Skeletal-Muscle Lesions

The pathological findings in the skeletal muscle are recorded in eight cases, on either biopsy ‡ or autopsy § material. In two reports the muscles were described as pale on gross inspection.‖ The microscopical descriptions closely resembled our own findings. The intensity of morphological alterations varied from case to case, apparently depending on the choice of biopsy site and the severity and chronology of the attack. There were swelling ¶ and patchy (segmental) regression # of muscle fibers; sequestration of fiber con-

References 6 and 23.
* References 4, 15, and 16.
† References 2, 3, 7-9, 16, 17, 19, and 20 and Stokes, W., cited by Acheson and McAlpine.[2]
‡ References 2, 6, 8, 17, and 19.
§ References 3, 4, and 15.
‖ References 6 and 15.
¶ References 15 and 19.
# References 4, 6, 15, and 18.

tents from the sheaths [6]; loss of staining * and of striation †; clumping of myofibrils [3]; waxy ‡ or hyaline [4] change, and vacuolization,§ fragmentation,‖ and liquefaction ¶ of the fiber contents. Regeneration was suggested by the finding of thin fibers with regimented or clumped sarcolemmal nuclei # and possibly by muscle giant cells.[15] Acute cellular exudation was lacking in all, although there was mild lymphocytic infiltration in some examples.* In one specimen [15] there was an increase of interstitial tissue with an increase in nuclei and a perimysial reaction. Another one,[8] obtained during a clinically free interval, showed an increase of sarcolemmal nuclei and a doubtful increase of the interstitial connective tissue. No changes were seen in blood vessels,[2] even in serial sections.[15] In one specimen the red cells in the capillaries had fused into hyaline thrombi.[3] Smooth and cardiac muscle seemed to escape the myoglobinolytic injury † The calcification of the necrotic muscle fibers observed in our Case 1 (Fig. 6) appears worthy of comment, particularly since the patient was in renal failure at the time the muscle biopsy was taken. That this has been reported in paroxysmal myoglobinuria only once before [15] may in part be related to the methods of fixation: acetic acid-Zenker's fixative will dissolve considerable amounts of calcium phosphate, as is mentioned in our first case report. Calcium phosphate in small amounts may also be dissolved by acidic formalin, which is used routinely in most pathological laboratories. This mineralization is probably a dystrophic calcification caused by a mechanism identical with that discussed by Gore [26] in relation to necrosis of the heart muscle—namely, renal failure, with consequent alterations of calcium and phosphate levels in the blood, together with local tissue necrosis, this combination resulting in deposition of insoluble tricalcium phosphate.

Myoglobinuria is preceded by and dependent upon myoglobin liberation from muscle, and the latter is associated with muscle necrosis. It is not known whether myonecrosis is the cause or the result of myoglobin liberation. On the one hand, it seems reasonable to believe that no muscle fiber can long survive once it has allowed the exit of myoglobin. On the other hand, it is hard to believe that muscle pigment could be retained once the fiber itself had become necrotic. The observations made here and those reported by others suggest that myoglobinuria results from muscle necrosis. Apparently gross myoglobinuria is dependent on the speed and intensity of the necrotizing process and on the amount of muscle involved.

Qualitative differences among various muscle groups with respect to their liability to necrosis may also play a role, as is suggested by the preferential affliction of the lower extremities over the upper ones, in both spontaneous and experimentally induced ‡ attacks of idiopathic myoglobinuria. Similarly, it is possible that in other myoglobinuric muscle disorders, such as Haff disease, crush injuries, etc., qualitative factors operate that allow particularly easy escape of myoglobin from the muscle and, consequently, rapid and marked accumulation of myoglobin in the urine. At any rate, quantitative and chronological considerations alone seem adequate to explain why certain muscle necroses not characteristically myoglobinuric, such as the anterior tibial syndrome, may at times eventuate in gross myoglobinuric discoloration of the urine. Conversely, the concept suggests that with tests more sensitive than those now available myoglobin might be demonstrated in the urine in necrotizing muscle disorders heretofore considered to be nonmyoglobinuric.

Isolated muscle fibers in idiopathic myoglobinuria may conceivably disintegrate between the clinically overt attacks. This is

* References 4 and 6.
† References 4, 6, and 15.
‡ References 3 and 15.
§ References 3 and 15.
‖ References 3, 4, and 15.
¶ References 3 and 4.
# References 2 and 15.
* References 2 and 6.
† References 3 and 4.

‡ References 9 and 19.

suggested by the second biopsy of our Case 2, which showed several small foci of degeneration although it was obtained after a three-month period during which no further clinical attack of pain or myoglobinuria had occurred. Similarly, we suspect that some fiber disintegration preceded the second attack of gross myoglobinuria in our Case 1, because the multinucleated muscle giant cells observed in the second biopsy specimen seem to be morphologically, topographically, and quantitatively independent of the fresh fiber necrosis. The history of muscle weakness preceding by many years the first paroxysm of overt myoglobinuria (our Case 1; Hipp and Shukers [9]) would also fit this concept. Hed,[8] who observed increased urobilinuria in two of his patients, considers a similar possibility:

> The increased proportion of urobilin in the urine is noticeable even between attacks. Urobilin may be interpreted as a breakdown product of myoglobin and accordingly indicates that myoglobin lysis is going on also between the acute attacks, although not in so great a degree that myoglobin appears in the urine.

Several considerations weaken the proposition § that the reported achromia of certain necrotic muscle fibers (also seen in the biopsy specimens of our two patients) accounts for the liberation of myoglobin. In the first place, there is no proof that the oxyphilia of normal muscle fibers is specifically due to their myoglobin content and hence no proof that lack of oxyphilia denotes escape of myoglobin. Secondly, no achromic fibers were demonstrated in the biopsy specimen of the second myoglobinuric episode of our first patient.

We believe that the histopathological observations of the muscle biopsy specimens of our two patients (Figs. 1 and 11), obtained on the 8th and 20th days of their respective myoglobinuric attacks and well after the disappearance of gross myoglobinuria, are in keeping with the concept here outlined. It has been pointed out above that neither the necrosis nor the reparative processes in different muscle fibers or even within different segments of the same fiber appeared to be uniform. Although this may indicate differences in susceptibility to a single short-lasting noxa, it may equally well denote a more sustained injury with successive waves of new muscle necrosis, or both.

§ References 4 and 6.

Fatal Cases

Four of the patients died, one directly of muscle necrosis in vital areas and three of the complication of acute tubular necrosis ("myoglobinuric nephrosis"). The 4-year-old boy described by Buchanan and Steiner [8] succumbed to respiratory-muscle paralysis two or three days after the onset of bulbar signs (he had difficulty in speaking and swallowing and ptosis of the eyelids). At autopsy his urinary bladder contained reddish-brown urine that was spectroscopically positive for myoglobin. He had had another attack two years previously. The patient described by Paul [15] was a 42-year-old woman who died of renal failure on the 15th day of her first attack. There were pigment casts in the renal tubules, and autopsy showed (uremic) pseudomembranous ileitis. Renal failure was responsible for the death of the 24-year-old man described by Bywaters and Dible,[3] who died on the seventh day of his third attack, and of the 23-year-old male patient of Schaar,[16] who died on the ninth day of what seems to have been his first attack.

Considerations Relating to Classification

Acheson and McAlpine [2] proposed a new classification of idiopathic myoglobinuria. They divided the reported cases into three groups: (1) idiopathic myoglobinuria in the narrower sense (five cases),‖ characterized by death in uremia during the first attack; (2) temporary muscular paralysis (seven cases),¶ characterized by muscular pain and weakness, and (3) muscular dystrophy (five cases),# characterized by symptoms such as atrophy of the shoulder girdle and hypertrophy of the calf muscles. There were several patients in the last group with blood

‖ References 4, 15, 16, and 27.

¶ References 5, 8, 10, and 11.

References 2, 12-14, and 20.

relatives who, though unaware of any myoglobinuria, apparently suffered from muscle wasting or pseudohypertrophic muscular dystrophy.

The validity of a nosologic separation between Groups 1 and 2 appears dubious, because, among other objections, it depends on the altogether fortuitous severity of acute tubular necrosis and death in renal failure. Similarly, the distinction made between Groups 2 and 3 is weakened by our Case 1, in which the patient displayed the earmarks of both—i. e. muscle atrophy with dystrophic symptoms together with muscular paralysis and pain during the myoglobinuric attack.

The validity of Group 3 as a nosologic entity seemingly does receive considerable support from the finding of muscle wasting in some of the myoglobinuric patients and also in their nonmyoglobinuric blood-relatives. However, this striking set of circumstances may have an explanation other than the one proposed by Acheson and others.* According to Adams and his co-workers,[1] the distinctive morphological manifestations of muscular dystrophy are absence of regenerative activity, increase in number of muscle nuclei, atrophy, splitting and great variability of the muscle fibers, and changes in the interstitium. The four biopsies from the thighs of our two patients showed none of the microscopical characteristics attributed to muscular dystrophy; moreover, the biopsies showed regenerative manifestations. Nor is the report of the muscle biopsy of Acheson's patient, who also belonged to Group 3, characteristic of muscular dystrophy. It must be concluded, therefore, that the proposed relation between true muscular dystrophy and the symptomatology of the Group 3 patients with paroxysmal attacks of myoglobinuria is not supported by anatomic evidence.

A possible solution of the problem of clinical similarities and familial associations suggestive of muscular dystrophy may perhaps be offered by the application of the concept previously outlined, i. e., that of the occurrence of subclinical attacks of myonecrosis without evident myoglobinuria. According to this hypothesis, the development of muscular wasting might be regarded as fortuitous and dependent on the intensity and frequency of subclinical attacks, on the one hand, and on the extent of muscle regeneration, on the other. Muscle wasting in blood-relatives might constitute an abortive form of myoglobinuria, i. e., the cumulative outcome of subclinical muscle necroses without liberation of myoglobin and, consequently, without pain, paresis, or overt myoglobinuria.

* References 6 and 23.

SUMMARY

Myoglobinuria is a sign of muscle necrosis due to a variety of causes, some known and others unknown (idiopathic).

In the idiopathic variety, which occurs in paroxysms, the myoglobinuric episode is characteristically but not invariably initiated by muscular effort. Twenty-one case reports in the literature are reviewed here, and two cases are added. It is apparent that there is no single pathogenic mechanism in this group of 23 cases. The common symptoms are muscle pain and weakness or paralysis typically involving the lower extremities but often involving other muscle groups as well, including those of deglutition, respiration, and speech. Urine discoloration by myoglobin is observed for one or more days after an attack and is recognized presumptively by the passage of urine that is free of erythrocytes but gives a positive benzidine reaction. Albuminuria and cylindruria commonly accompany myoglobinuria. There is no discoloration of the blood plasma.

The disease has its onset during childhood in one-third of the cases. Those patients whose first myoglobinuric paroxysm is observed after age 14 often have a history of muscular weakness and aching going back to childhood or early youth.

Four of the twenty-three patients died—one of respiratory failure due to necrosis of the respiratory muscles and three of acute tubular necrosis of the kidneys ("lower nephron nephrosis," "myoglobinuric nephrosis") and renal insufficiency. The two patients here reported survived, but the course

of each was complicated by a period of renal insufficiency.

Histologically, idiopathic paroxysmal myoglobinuria is characterized by muscle necrosis which does not cause exudative phenomena. Pathological evidence indicates that muscle necrosis occurs not only during but also between overt attacks of myoglobinuria. This may explain the association of idiopathic paroxysmal myoglobinuria with muscular atrophies in these patients; it may also explain the finding of muscular atrophies in their nonmyoglobinuric blood-relatives. There is no pathological evidence that the disease has any relation to the muscular dystrophies.

Dr. Harry A. Derow made available the clinical record of Case 1. Dr. Raymond D. Adams reviewed the microscopical slides of both cases here reported and made helpful suggestions.

ADDENDUM

Two further case reports have come to our attention recently. The first (Berenbaum, M. C.; Birch, C. A., and Moreland, J. D.: Paroxysmal Myoglobinuria, *Lancet* **1**: 892, 1955) was that of 10-year-old girl admitted to the hospital because of pains in legs and abdomen, vomiting, and leucocytosis. Biopsy of skeletal muscle was obtained on the fourth day of the disease: The histological changes, including calcification of degenerated fibers, were identical with those described by us. There were loss of glycogen and β-metachromasia, increase and uniform distribution of phosphatides, patchy to complete loss of myoglobin (negative reactions to Pickworth's benzidine stain), and loss of birefringence. Myoglobin content of diseased muscle was reduced to one-seventh of normal. The authors suggest that an abnormal myoglobin may play a role in the pathogenesis of paroxysmal myoglobinuria.

The second case (Fletcher, W. D., and Prankard, T. A. J.: Paroxysmal Myoglobinuria, Letters to the Editor, *Lancet* **1**: 1072, 1955) was that of a 21-year-old man whose attacks were precipitated by the combined action of cold and exertion. By electrophoretic examination no difference was detected between the myoglobin of the patient and that of normal control material.

REFERENCES

1. Adams, R. D.; Denny-Brown, D., and Pearson, C. M.: Diseases of Muscle: A Study in Pathology, New York, Paul B. Hoeber, Inc., 1953.

2. Acheson, D., and McAlpine, D.: Muscular Dystrophy Associated with Paroxysmal Myoglobinuria and Excessive Excretion of Ketosteroids, Lancet **2**:372, 1953.

3. Buchanan, D., and Steiner, P. E.: Myoglobinuria with Paralysis (Meyer-Betz Disease): Report of a Case, A. M. A. Arch. Neurol. & Psychiat. **66**:107, 1951.

4. Bywaters, E. G. L., and Dible, J. H.: Acute Paralytic Myohaemoglobinuria in Man, J. Path. & Bact. **55**:7, 1943.

5. Debré, R.; Gernez, C., and Sée, G.: Crises myopathiques paroxystiques avec hémoglobinurie, Bull. et mém. Soc. méd. hôp. Paris **50**:1640, 1934.

6. Elek, S. D., and Anderson, H. F.: Paroxysmal Paralytic Myoglobinuria, Brit. M. J. **2**: 533, 1953.

7. Hed, R.: En familjär form av paroxysmal myoglobinuri, Nord. med. **35**:1586, 1947.

8. Hed, R.: Myoglobinuria, A. M. A. Arch. Int. Med. **92**:825, 1953.

9. Hipp, H. R., and Shukers, C. F.: Spontaneous Myoglobinuria: Report of a Case with Symptoms of Myotonia, Ann. Int. Med. **42**:197, 1955.

10. Hittmair, A.: Haemoglobinuria paroxysmalis paralytica, Wien. klin. Wchnschr. **38**:431, 1925.

11. Huber, J.; Florand, J.; Lièvre, J. A., and Néret: Crises myopathiques paroxystiques avec hémoglobinurie, Bull. et mém. Soc. méd. hôp. Paris **54**:725, 1938.

12. Kreutzer, F. L.; Strait, L.; Kerr, W. J., and Hrenoff, M. K.: Spontaneous Myohemoglobinuria in Man, Arch. Int. Med. **81**:249, 1948.

13. Louw, A., and Nielsen, H. E.: Paroxysmal Paralytic Hemoglobinuria, Acta med. scandinav. **117**:424, 1944.

14. Meyer-Betz, F.: Beobachtungen an einem eigenartigen mit Muskellähmungen verbundenen Fall von Hämoglobinurie, Deutsch. Arch. klin. Med. **101**:85, 1911.

15. Paul, F.: Über einen Fall von paralytischer Hämoglobinurie beim Menschen, Wien. Arch. inn. Med. **7**:531, 1924.

16. Schaar, F. E.; LaBree, J. W., and Gleason, D. F.: Paroxysmal Myohemoglobinuria with Fatal Renal Tubular Injury, J. Lab. & Clin. Med. **34**: 1744, 1949.

17. Schaar, F. E.: Paroxysmal Myoglobinuria, A. M. A. Am. J. Dis. Child. **89**:23, 1955.

18. Scherwin, J.: Myoglobinuria paralytica, Nord. med. **25**:460, 1945.

19. Spaeth, T. H.; Rosenthal, M. C., and Damashek, W.: Idiopathic Myoglobinuria in Man, Blood **9**:881, 1954.

20. Wissler, H.: Paroxysmale Myoglobinurie, Helvet. pædiat. acta **3**:334, 1948.

21. Millikan, G. A.: Muscle Hemoglobin, Physiol. Rev. **19**:503, 1939.

22. Fleming, R. G., and Kinsman, J. M.: March Hemoglobinuria, South. M. J. **38**:739, 1945.

23. Biörck, G.: On Myoglobin and Its Occurrence in Man, Acta med. scandinav. (Supp. 226) **133**:1, 1949.

24. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effect of Electrically Induced Convulsions on Peripheral Venous Pressure in Man, Arch. Neurol. & Psychiat. **58**:193, 1947.

25. Lowenbach, H., and Greenhill, M. H.: The Effect of Oral Administration of Lactic Acid upon the Clinical Course of Depressive States, J. Nerv. & Ment. Dis. **105**:343, 1947.

26. Gore, I., and Arons, W.: Calcification of the Myocardium: A Pathologic Study of 13 Cases, Arch. Path. **48**:1, 1949.

27. Günther H.: Kasuistische Mitteilung über Myositis myoglobinurica, Arch. path. Anat. **251**: 141, 1924.

28. Berlin, R.: Haff Disease in Sweden, Acta med. scandinav. **129**:560, 1947.

Mecamylamine, a New, Orally Effective, Hypotensive Agent

Experimental and Clinical Evaluation

EDWARD D. FREIS, M.D.
and
ILSE M. WILSON, M.D., Washington, D. C.

Stone and his co-workers * have reported recently on certain unusual pharmacological properties of mecamylamine (3-methylaminoisocamphane) hydrochloride. This compound, a secondary amine, produces a marked and prolonged degree of blood pressure reduction and ganglionic blockade in animals. Mecamylamine also is well absorbed from the gastrointestinal tract, the L. $D._{50}$ being approximately the same whether the drug is adminished subcutaneously or orally. By contrast, previously successful ganglion-blocking agents, which are tertiary amines, are poorly absorbed from the gastrointestinal tract. The ratio of oral to subcutaneous hypotensive dosages of the latter drugs in man is approximately 15 : 1.†

In patients under treatment with ganglion-blocking agents it is possible that some of the difficulties of clinical management, such as irregular fluctuations of blood pressure and gastrointestinal atony, may be due to the poor absorption and, hence, large local accumulations of the previously available compounds in the gastrointestinal tract. It seemed worth while, therefore, to evaluate the use of mecamylamine, a readily absorbed blocking agent, in hypertensive patients.

MATERIALS AND METHODS

The subjects for the experimental studies were patients from the wards of the Georgetown University and the Veterans Administration Hospitals, Washington, D. C. The methods of investigation used were similar to those published in a previous communication.[3] Mecamylamine was administered in sterile water containing 1.0 mg. of active substance per milliliter.

In the clinical studies the patients were chosen from the wards and hypertensive clinics of the above hospitals. They represented a mixed group of severe hypertensives, white and Negro, representing all varieties of social and economic classes.

EXPERIMENTAL RESULTS

Comparison of Intravenous and Oral Dosages

The blood pressure response in both the supine and erect positions was followed in nine patients given single intravenous doses of 15 to 20 mg. of mecamylamine. The next day the same patients were given an oral dose which was 5 to 10 mg. less than the previous intravenous dose. Following all doses there was a significant reduction of supine blood pressure and a marked postural hypotension, which was as great after oral as after intravenous administration (Table 1). These results, in marked contrast to the relatively large oral dosages required with other

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Mecamylamine was supplied under the trade name of Inversine by John R. Beem, M.D., Sharp & Dohme.

From the Cardiovascular Research Laboratory, Georgetown University Hospital, the Department of Medicine, Georgetown University School of Medicine, and the Veterans Administration Hospital.

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* Stone, C. A.; Torchiana, M. L.; O'Neill, G. P., and Beyer, K. H.: Ganglionic Blocking Properties of 3-Methylaminoiso-Camphane Hydrochloride (Mecamylamine), a Secondary Amine, read before the American Society for Pharmacology and Therapy, Iowa City, Sept. 7, 1955.

† References 1 and 2.

TABLE 1.—*Comparative Hypotensive Effects of Single Intravenous and Single Oral Doses of Mecamylamine*

	Intravenous					Oral				
		Arterial Pressure, Mm. Hg					Arterial Pressure, Mm. Hg			
		Before		After			Before		After	
Case	Dose, Mg.	Supine	Erect	Supine	Erect	Dose, Mg.	Supine	Erect	Supine	Erect
1	20	190/120	180/125	130/90	90/80	10	170/115	160/115	135/90	100/75
2	15	180/110	190/110	130/85	110/70	10	150/92	146/92	120/85	98/70
3	15	190/120	180/130	140/105	120/98	10	190/130	190/130	170/110	150/112
4	20	190/115	190/120	140/95	115/90	10	170/122	168/124	146/102	148/102
5	20	240/160	230/160	180/140	150/120	10	190/140	186/130	160/118	156/110
6	20	200/130	198/135	150/100	130/90	10	205/125	200/135	160/110	150/100
7	20	200/115	190/120	160/98	140/90	10	170/110	160/115	140/90	110/70
8	20	220/115	200/120	160/100	102/75	15	210/120	160/100	145/80	80/60
						10	220/120	160/110	160/90	115/80
9	20	230/120	200/120	160/100	100/60	15	210/100	150/100	100/70	80/60
						10	200/110	170/110	150/90	90/70
						5	200/110	160/110	155/100	120/80

ganglion-blocking agents, provided clear evidence that mecamylamine is well absorbed from the human gastrointestinal tract.

Following intravenous administration, the blood pressure began to fall gradually several minutes after injection, reaching minimum values in one-half to one hour. It remained at the lowest level for several hours or, in others, began to rise after one hour reaching control values in all cases by 6 to 12 hours.

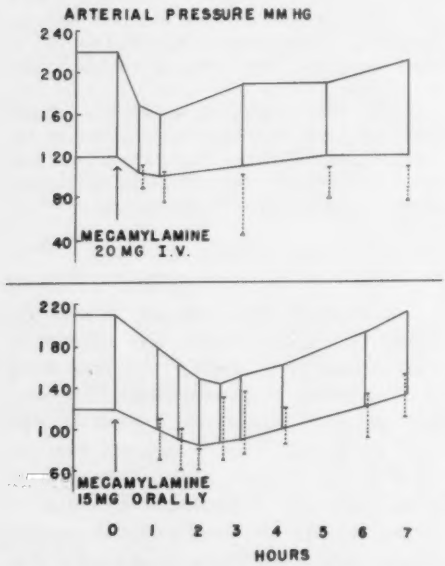

Fig. 1.—Charts showing characteristic blood pressure response to 20 mg. of mecamylamine intravenously (above) and 15 mg. orally (below) in a 62-year-old man with essential hypertension. The tests were carried out on successive days. The broken vertical columns indicate the blood pressure in the erect position. See text for further details.

The postural hypotension usually followed a similar time pattern (Fig. 1).

Following oral dosage, the blood pressure began to fall after 1 hour, reached minimum values at approximately 2 hours, and returned gradually to control values in 4 to 12 hours. The more profound the reduction of blood pressure the longer the duration of the response. Postural hypotension sometimes persisted for several hours after the blood pressure in the supine position had returned to control levels.

Effect of Mecamylamine on Sympathetic Vasoconstrictor Reflexes

Previous studies with the ganglion-blocking agent hexamethonium demonstrated a marked inhibition or abolition of homeostatic vasoconstrictor reflexes.[3] Postural hypotension alone does not indicate such inhibition, since peripheral vasodilators acting directly on blood vessels, such as sodium nitrite, may induce a postural fall of blood pressure.

Four criteria were used to measure the reactivity of the sympathetic vasoconstrictor responses and the effect of mecamylamine thereon. These were the hypertensive overshoot following the Valsalva maneuver,[4] the cold pressor test,[5] the skin temperature gradient between the digits and the umbilicus in patients exposed in a cold constant-temperature room,[6] and reflex vasoconstrictor responses as revealed by digital plethysmography.[7]

(*a*) *The Valsalva Maneuver.*—If a patient blows out forcibly into a closed tube for 10

TABLE 2.—*Vasopressor Responses to the Valsalva Maneuver Before and After the Intravenous Administration of Mecamylamine*

		Control				After Mecamylamine		
		Arterial Pressure, Mm. Hg				Arterial Pressure, Mm. Hg		
Case	Dose, Mg.	Basal	After Valvalsa	Overshoot,* %	Time After Drug, Min.	Basal	After Valsalva	Overshoot,* %
1	20	263/142	288/142	20	10	228/128	253/160	15
					40	240/150	260/162	9
4	20	201/98	240/125	18	10	160/88	174/95	8
					40	162/90	173/98	7
7	20	225/111	253/160	20	2	210/98	232/110	12
					30	190/84	204/88	6
3	15	194/110	290/160	47	10	180/114	225/136	22
					40	174/114	218/135	22
2	15	168/90	190/98	11	10	142/82	133/76	0
					40	140/80	134/74	0
5	20	262/160	310/188	18	10	225/145	274/172	24
					30	218/150	298/180	29
					50	222/160	270/178	17
					120	210/150	232/156	7

* Calculated from the mean (one-half the sum of the systolic and diastolic) pressure.

seconds, intrathoracic pressure is markedly increased and the blood pressure will fall. When the expiratory effort suddenly is released there is a transient overshoot of blood pressure above the basal level. Wilkins has presented evidence that the pressor overshoot is due primarily to reflex vasoconstriction mediated over sympathetic pathways.[4] After lumbodorsal splanchnicectomy [4] or certain "sympatholytic" agents ‡ the overshoot is abolished.

The Valsalva overshoot was determined in six patients before and periodically for one hour after intravenous mecamylamine, with use of direct continuous recording of arterial pressure [3] (Table 2). The overshoot was abolished in one of the six cases and reduced by 50% to 70% in the remaining subjects.

(*b*) *The Cold Pressor Test.*—The blood pressure response during one minute of immersion of the patient's hand in ice water was determined before and one-half hour after intravenous mecamylamine. After the drug the cold pressor response was significantly reduced in only two of the six patients (Table 3).

(*c*) *The Skin Temperature Gradient.*—Nine hypertensive patients, who had no evidence of peripheral vascular disease, were exposed to room temperatures of 63 to 71 C. In any one experiment the room temperature was kept constant within a range of 3 C. The skin temperature of the digits and umbilicus was recorded every three minutes. After one hour mecamylamine was given intravenously and the skin temperature and blood pressure values were recorded for an additional hour.

The results followed no consistent pattern (Table 4). In three patients there was a significant elevation of toe temperature; in four, a partial rise, and in two there was no significant change. There was a significant rise

‡ References 3 and 5.

TABLE 3.—*Effect of Intravenous Mecamylamine on the Responses to the Cold Pressor Test*

	Arterial Pressure, Control			Arterial Pressure After Mecamylamine*		
Case	Basal, Mm. Hg	Peak Response to Ice, Mm. Hg	Increase,† %	Basal, Mm. Hg	Peak Response to Ice, Mm. Hg	Increase,† %
1	262/142	300/164	15	232/142	264/166	12
4	194/98	218/112	13	166/95	188/110	14
7	232/100	240/108	5	210/94	218/98	3
3	154/98	188/108	17	174/110	190/120	9
2	198/100	256/138	32	166/98	214/120	28
5	274/156	280/166	3	222/160	225/156	0

* The post-treatment tests were carried out approximately one-half hour after administration of mecamylamine. For dosages see Table 1.
† See footnote, Table 1.

TABLE 4.—*Changes in Skin Temperatures After the Intravenous Administration of Mecamylamine*

		Control						After Mecamylamine					
		Blood Pressure, Mm. Hg		Skin Temp., F*				Blood Pressure, Mm. Hg		Skin Temp., F*			
Case	Dose, Mg.	Supine	Erect	R	U	T	F	Supine	Erect	R	U	T	F
10	15	195/115	190/115	68	94	69	72	166/100	140/95	68	91	71	87
11	10	190/110	190/110	69	94	69	74	150/95	120/90	70	94	76	88
9	20	230/120	200/115	63	90	77	66	160/108	110/80	65	87	87	66
12	20	190/135	188/120	68	88	66	70	166/120	150/115	68	82	82	69
13	18	190/125	190/120	70	95	77	77	158/108	140/100	70	94	86	83
14	28	240/135	230/120	70	91	76	79	170/110	130/120	70	92	80	87
15	16	180/110	180/108	71	86	73	84	130/105	130/100	71	88	79	85
16	12	130/90	130/88	67	93	68	74	115/90	100/80	67	94	78	91
17	15	120/75	120/75	71	88	73	85	105/72	90/80	71	86	86	95

* R, room temperature; U, umbilicus temperature; T, toe temperature; F, finger temperature.

in finger temperature in five cases and an insignificant change in four.

(*d*) *Digital Plethysmography.*—Following a deep inspiration there is normally a sharp decrease in the volume of the digit and the digital pulse, indicating vasoconstriction. This reflex vasoconstriction, which can be detected readily in the digital plethysmograph, is abolished after sympathetic denervation [7] and after hexamethonium.[8]

During the period of observation, which lasted 30 to 60 minutes following intravenous mecamylamine, there was a partial inhibition of the vasoconstrictor response to a deep inspiration in two cases and no change in four (Table 5). To one of these patients hexamethonium, 50 mg., was given intravenously, with an immediate abolition of the vasoconstrictor reflex (Fig. 2). Because of the possibility that insufficient time was allowed to permit the development of sympathetic blockage, three patients under continous oral administration of mecamylamine were studied. These showed a persistence of digital reflex vasoconstriction despite significant reductions of blood pressure and marked postural hypotension.

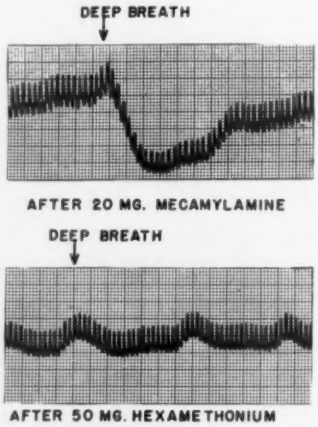

Fig. 2.—Tracings of the digital plethysmograph in a 39-year-old man with essential hypertension. The upper tracing shows an active vasoconstrictor response following deep inspiration 40 minutes after 20 mg. of mecamylamine. The lower tracing was taken 10 minutes after 50 mg. of hexamethonium in the same patient. The vasoconstrictor response is completely blocked, the fluctuations in base line being due to respiratory movement.

CLINICAL RESULTS

EFFECT OF CONTINUOUS ORAL ADMINISTRATION ON BLOOD PRESSURE

Thirty-six patients with "fixed" moderately severe to severe hypertension were

TABLE 5.—*Effect of Mecamylamine on Digital Vasoconstrictor Reflexes*

		Control			After Mecamylamine				
		Blood Pressure, Mm. Hg			Blood Pressure, Mm. Hg		Vasoconstrictor Reflexes, Time After Drug, Min.			
Case	Dose, Mg.	Supine	Erect	Vasoconstrictor Reflexes	Supine	Erect	2	10	30	60
10*	20	200/130	170/130	++++	180/130	Not taken	++++	++++	+++	.....
18	10	160/110	160/110	+++	130/98	100/80	+++	+++	+++	+++
19	20	190/120	190/125	+++	160/110	140/100	+++	+++	+++	.....
20	18	190/125	190/120	++	150/115	130/100	++	++	++	.....
21	20	120/75	120/75	++++	95/70	95/70	++	++	++	+++
22	5	100/65	100/65	+++	90/50	95/50	++	+++	++	+++

* Hexamethonium, 50 mg. intravenously, while producing no further reduction of supine blood pressure, completely abolished the vasoconstrictor response in this patient.

treated continuously with oral mecamylamine for periods varying from one to four months (average, 2.8 months). The Keith, Wagener, and Barker classification of the optic fundi [8] in these patients prior to any treatment was as follows: Grade IV, 8 patients; Grade III, 15 patients; Grade II, 13 patients, and Grade I, no patients (Table 6).

For the group as a whole the mean pretreatment blood pressure was 217/129 mm. Hg. After treatment the mean blood pressure was 167/108 in the supine position and 153/101 in the erect position. This represented a reduction of 21% systolic and 16% diastolic in the supine position and of 27% systolic and 20% diastolic in the erect position. In every case the control and posttreatment blood pressure values were the average of many obtained in the hospital, by the patient's families in the home, and in the clinic.

Dosage

The average total daily dose was 29 mg. (range, 3 to 90 mg.). In general, this was divided into three doses per day, generally at 8 a. m., 2 p. m., and 10 p. m. However, some patients exhibited such a prolonged effect from the drug and were so sensitive to it in the morning hours that the dose taken the night previously controlled their blood pressure until the early afternoon. In such cases, only two doses per day were required, at noon and at bedtime. Other patients exhibited resistance to the drug during the evening hours and so required an extra dose at 5 or 6 p. m.

Table 6.—*Average Blood Pressure Before and After Treatment with Mecamylamine in Thirty-Six Hypertensive Patients*

Case	Age, Yr.	Sex	Optic Fundi, Grade	Control B. P., Mm. Hg	Daily Dose, Mg.	Duration, Mo.	Post-Treatment Blood Pressure, Mm. Hg		Per Cent Decrease			
									Supine		Erect	
							Supine	Erect	Systolic	Diastolic	Systolic	Diastolic
1	57	M	III	200/135	3	3	160/105	150/102	20	22	25	24
2	41	M	III	200/130	32.5	3.5	150/110	130/100	24	15	35	23
3	42	M	II	180/120	5	2.5	168/110	154/100	6	8	14	16
4	39	M	III	220/130	3	3.5	145/110	125/105	34	15	43	19
5	59	M	II	180/120	32.5	3	140/95	120/90	22	20	33	25
6	43	M	III	240/135	25	2.5	172/116	152/106	28	14	36	21
7	39	M	III	200/130	25	2.5	180/108	170/100	10	17	15	23
8	39	M	III	200/135	20	3.5	170/120	140/115	15	11	30	15
9	45	M	II	190/120	25	3	160/105	150/100	16	13	21	17
10	61	M	III	198/125	40	3.5	150/100	120/90	24	20	39	28
11	47	M	II	220/135	27.5	4	180/115	170/110	18	15	22	19
12	38	M	II	185/130	30	3.5	170/120	160/115	8	7	14	19
13	59	M	IV	220/140	55	4	200/115	170/110	9	18	23	21
14	62	M	III	200/115	32.5	3	180/110	170/105	10	4	15	9
15	43	M	III	200/135	10	3.5	170/120	150/110	15	11	25	19
16	37	M	II	190/135	27.5	3	140/102	135/100	26	23	28	26
17	45	M	III	210/120	27.5	2.5	170/112	170/115	19	6	19	4
18	65	M	III	200/140	25	2.5	150/110	150/110	25	21	26	21
19	54	M	II	210/115	3	1	150/98	135/90	28	15	35	22
20	62	M	IV	220/130	40	1.5	205/105	197/105	6	19	10	19
21	29	M	IV	200/150	32.5	2	180/115	170/110	10	23	15	27
22	49	F	II	230/130	40	3	170/100	160/100	26	23	30	23
23	53	M	II	200/120	50	3.5	168/110	160/108	16	8	20	10
24	45	F	IV	230/130	15	3.5	170/105	160/100	26	19	31	23
25	31	F	III	250/140	25	3.5	155/100	150/98	38	28	40	30
26	58	M	IV	230/130	50	2	180/110	160/105	21	15	30	19
27	55	M	II	230/120	35	2	175/110	168/105	24	8	27	13
28	40	F	II	220/120	30	4	158/108	150/110	28	10	31	8
29	48	M	IV	210/120	10	3.5	155/100	150/95	26	17	28	20
30	39	F	II	260/150	40	3	160/105	155/100	38	30	40	33
31	59	M	II	220/140	22	3.5	190/115	180/110	14	17	18	21
32	45	M	III	220/150	90	2	182/112	170/108	17	25	23	28
33	50	M	III	235/135	47.5	1	200/110	210/112	14	19	11	17
34	55	M	IV	230/130	15	1	170/110	130/95	26	15	43	27
35	55	F	III	230/120	80	3	165/98	120/80	28	18	47	33
36	58	M	IV	240/130	40	1	150/100	130/95	37	23	45	27
Mean				217/129	29	2.8	167/108	153/101	21	16	27	20

There also was evidence for some cumulative effects of mecamylamine. It was not uncommon on discontinuing the drug to observe a gradual disappearance of the hypotensive effects over a period of 24 to 72 hours. When dosages were being adjusted it often was found that the maximum effect from an elevation of dosage would appear on the second day of treatment at the new level, suggesting that some cumulation had occurred from the previous day.

On the basis of these experiences we are at present beginning therapy with a dose of 2 mg. after breakfast, at 2 p. m., and at bedtime and then increasing the dosage by 2 mg. every 48 hours, until a hypotensive effect is obtained. At this point the three doses during the day are individually raised or lowered as the occasion demands so as to obtain the least diurnal fluctuation of blood pressure within the limits of tolerable side-effects. An additional dose may be given at 5 or 6 p. m. if the evening pressures are high, or the morning dose may be sharply reduced or omitted if the blood pressure is extremely low at that time. A running record of the supine and erect blood pressure values in the hospital and later at home was found to be essential in determining the need and extent of such modifications.[9]

Other Clinical Effects

(*a*) *Optic Fundi.*—Of the eight patients who exhibited Grade IV changes in the optic fundi prior to treatment, two reverted to Grade III and six to Grade II. In the group of 15 patients with Grade III fundi, 1 remained Grade III, 13 reverted to Grade II, and 1 reverted to Grade I. In the Grade II cases seven remained Grade II and six reverted to Grade I.

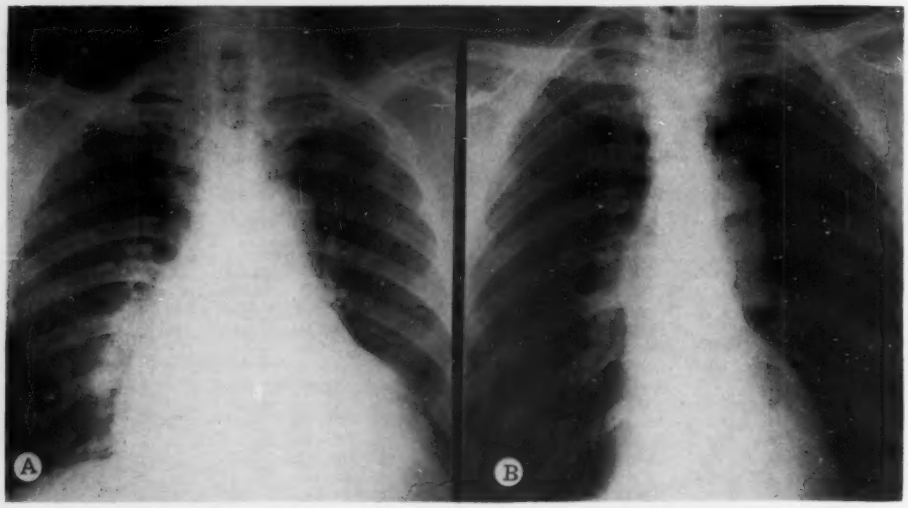

Fig. 3.—Roentgenograms of the chest taken before and three months after treatment with mecamylamine in a 57-year-old Negro man with malignant hypertension. Digitalis and mercurial diuretics were not used in treating this patient.

(*b*) *Cardiac Status.*—Cardiac size was measured roentgenographically before and after treatment in 31 cases. Only changes of 1 cm. or more in the transverse diameter of the heart were considered significant, since the depth of inspiration and other factors may influence the apparent size. Three cases showed an increase in transverse diameter ranging between 1.5 and 2.0 cm. (mean, 1.8 cm.). Twenty-one exhibited no change, while seven showed a decrease varying between 1 and 3 cm. (mean, 1.7 cm.) (Fig. 3).

Electrocardiographic changes were followed in 30 cases. Left ventricular hypertrophy was indicated in the electrocardio-

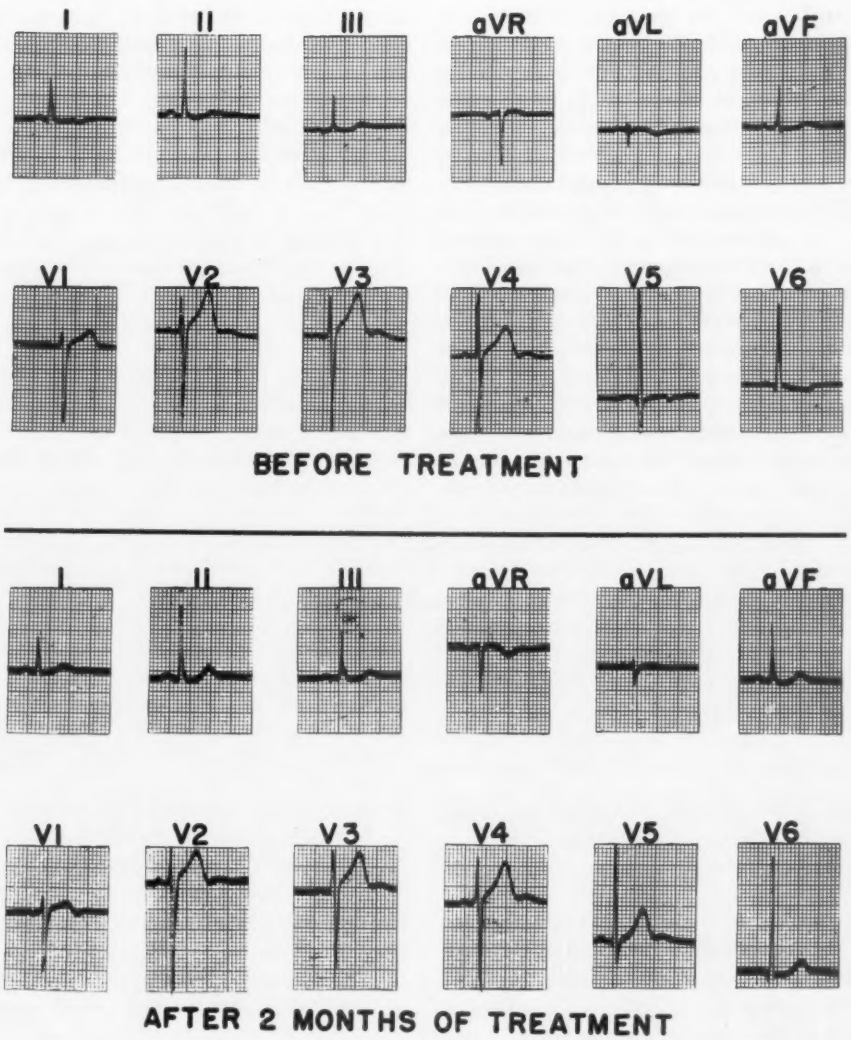

Fig. 4.—Cuttings taken from electrocardiograms of a 45-year-old man with essential hypertension. After two months of treatment with mecamylamine the pattern of left ventricular hypertrophy disappeared.

grams of 28 patients. Of this number, 23 were unchanged, 4 reverted to normal (Fig. 4), and 1 exhibited changes toward normal. Two patients with normal electrocardiograms before treatment showed no change after therapy.

(c) Renal Function.—Albuminuria tended to lessen after treatment in the patients who showed the greatest amounts of albumin before therapy (Table 7). In the patients with lesser degrees of albuminuria the changes were variable. In the 28 cases in which albuminuria was measured, 11 exhibited improvement, 11 were unchanged, and 6 showed a greater degree of albuminuria than before treatment. There were no significant changes in specific gravity or in the urinary sediments.

In 22 cases the excretion of phenolsulfonphthalein (PSP) dye was measured in a sample collected 15 minutes after the dye was injected. A change of 5% excretion or more was considered significant. Ten patients showed a mean decrease of 11% of dye excretion following treatment; seven exhibited no change, while in five patients there was a mean increase of 12% of dye excreted.

The blood urea nitrogen level was measured in 28 cases before and after therapy. Nine exhibited elevations of blood urea nitrogen concentration before treatment, the levels varying between 26 and 51 mg. per 100 cc. In five of these patients the BUN decreased to the normal range after therapy, and in one it changed toward but not to normal. In two cases there was no significant change, while in one, who had the highest level before treatment, there was an increase from 51 to 76 mg. per 100 cc.

Side-Effects

The commonest side-effect encountered was constipation, which occurred in 32, or 88%, of the patients (Table 8). In all except three of these the constipation could be controlled by giving neostigmine, 15 to 45 mg. orally, before breakfast and/or laxatives such as cascara sagrada or magnesium hydroxide. Impaired visual accommodation and postural faintness each occurred in 10, or 27%, of the cases. Impotence was complained of in 10 patients; it was partial in 4 and complete in 6. Difficulty in emptying the urinary bladder and dry mouth were common, each occurring at some time during treatment in nearly 30%. The urinary difficulty usually was mild, consisting only of diminution of the urinary stream. In two cases there was inability to empty the bladder completely, characterized by repeated small frequent voidings. This cleared later in both patients. Dryness of the mouth due to inhibition of salivary gland secretion occurred in 7 of the patients early in treatment and in 11, or 30%, of the cases at some time later in the course of treatment. In general, the side-effects did not tend to disappear over the relatively short period of this study.

"Tolerance"

The extent of "tolerance" was estimated by comparing the dosage requirement early and late in treatment. Over the period of therapy with mecamylamine, varying from one to four months, there was no increase in

Table 7.—*Changes in Degree of Albuminuria After Mecamylamine in Twenty-Eight Cases*

Degree of Albuminuria Before Treatment	Patients, No.	Degree of Albuminuria After Treatment					
		++++	+++	++	+	Tr.	Neg.
++++	2	..	..	1	..	1	..
+++	1	..	..	..	1	..	..
++	4	1	..	1	1	..	1
+	7	..	..	.	4	2	1
Tr.	8	..	1	1	1	2	3
Neg.	6	..	..	..	.	2	4

Table 8.—*Incidence of Side-Effects Occurring in Thirty-Six Hypertensive Patients Under Continuous Treatment with Oral Mecamylamine*

Side-Effect	Early in Treatment		After 1 to 4 Mo.	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Constipation	32	88	3	8
Mild	11	..	..	..
Moderate	15	..	..	..
Severe	6	..	..	..
Constipation controlled with laxatives and/or neostigmine	..	..	28	77
Impaired visual accommodation	10	27	8	22
Dry mouth	7	19	11	30
Impotence	..	..	10	27
Incomplete	..	..	4	..
Complete	..	..	6	..
Postural faintness	10	27	9	25
Postural syncope	1	3	4	11
Difficulty in emptying urinary bladder	7	19	11	30
Mild	5	..	7	..
Moderate	1	..	4	..
Severe	1	..	0	..

dosage in 19, or 53%; in 10 of these the dosage requirement actually lessened (Table 9). In 12, or 33%, an increase of 5 to 20 mg. in the total daily dosage was required. In five patients the dosage increase was greater than 20 mg. per day. During the period of this study, therefore, in the majority of cases the development of tolerance was slight or nonexistent.

TABLE 9.—*Extent of "Tolerance" to Oral Mecamylamine: Change in Daily Dosage Requirement After One to Four Months of Treatment*

Change in Daily Dosage Requirement	No. Patients	Per Cent of Total
More than 5 mg. decrease	10	28
No essential change	9	25
Between 5 and 20 mg. increase	12	33
More than 20 mg. increase	5	14
Total	36	100

Treatment Failure and Complications

Three patients died either while under treatment or shortly thereafter. Two of these had malignant hypertension with uremia. Both exhibited significant but not excessive reduction of blood pressure and a decreased urinary output. The blood urea nitrogen rose in one case and decreased slightly in the other. Autopsy revealed advanced malignant nephrosclerosis in both instances.

The third patient was a 55-year-old man with long-standing hypertensive heart disease. The blood pressure had been reduced from 230/120 to approximately 170/110 mm. Hg, with apparent improvement in cardiac decompensation. After six weeks of treatment, while at home, he suddenly was seized with severe substernal pain and died two hours later. The clinical impression was myocardial infarction; autopsy was not obtained.

Treatment was discontinued in four patients because of abdominal distention and vomiting, either with obstipation or with small frequent liquid stools diagnosed as a low-grade paralytic ileus. These symptoms cleared promptly on discontinuation of therapy. In one case it was possible to resume treatment in reduced dosage without recurrence. In another patient two later attempts at therapy were followed again by symptoms of ileus.

Treatment was discontinued in another uremic patient with malignant hypertension because of severe postural hypotension with syncope, decreased urinary output, and increasing uremia. This patient improved when veratrum was substituted for mecamylamine, although the blood pressure level rose. Treatment was discontinued in a 57-year-old-man because of severe postural hypotension with increased angina and in a 59-year-old man because of difficulty in emptying the urinary bladder and severe dryness of the mouth not relieved by oral pilocarpine nitrate.

One patient developed acute appendicitis after one month of therapy. He was operated upon, and recovery was uneventful. Another patient with congestive heart failure and massive ascites failed to respond to mecamylamine, even in large doses, until paracentesis was performed. After removal of the ascitic fluid the blood pressure fell from 220/120 mm. Hg to nearly normotensive levels on a total daily dose of 20 mg. of mecamylamine. He has remained clear of congestive heart failure and ascites over a three-month period. It is suggested that the tight ascites produced sufficient abdominal compression to overcome the vasodilator effects of the mecamylamine in the splanchnic area.

Addition of Other Hypotensive Agents

In assessing the effect of the addition of other agents the blood pressures were determined three to five times per day either in the hospital or at home. The average of the blood pressure values for the week immediately preceding and immediately following the change in medication were averaged and compared.

(a) Addition of Hydralazine.—The hypotensive effect of hydralazine when added to mecamylamine was tested in 13 patients. The daily dosage of hydralazine varied between 75 and 200 mg. per day, the average dose being 100 mg. per day. In three of these cases an additional hypotensive effect was observed. The reduction was not great, vary-

ing between 10% and 14% below the values obtained with mecamylamine alone. In the remaining 10 patients no additional hypotensive effects were observed following hydralazine. Two patients developed mild headaches; one, mild palpitation, and one, severe palpitation. These side-effects were transient. It is possible that the addition of hydralazine might have produced additional hypotensive effects in a greater number of patients if it had been given in larger doses. Such increases in dosage were not attempted, however, because of the possibility of developing collagen vascular syndromes.[10]

(b) Addition of Reserpine.—Reserpine was added to the regimen of 11 patients in dosages of 0.25 to 1.0 mg. (mean, 0.5 mg.) per day. In 5 of the 11 cases additional reductions of blood pressure occurred, varying between 9% and 25% below the values obtained with mecamylamine alone. Among these five patients, one experienced nasal stuffiness while the remaider had no side-effects attributable to reserpine.

Comparison of Mecamylamine and Pentolinium Tartrate

In 19 patients who had been under treatment with pentolinium tartrate for six months or longer the drug was discontinued and mecamylamine was substituted. The daily dosages of pentolinium tartrate had varied between 60 and 1150 mg. (average, 580 mg.). This had resulted in reductions of "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure averaging 16% in the supine and 20% in the erect position.

The daily dosages of mecamylamine in the same group of patients varied between 3 and 90 mg. (average, 35 mg.). In general, the patients who required the higher dosages of pentolinium tartrate also needed the largest daily requirement of mecamylamine. The reductions of mean blood pressure averaged 21% in the supine and 25% in the erect position.

When asked which medication they preferred, 14 favored mecamylamine. The chief reason given was that the blood pressure reduction was more uniform from morning to night and from day to day with mecamylamine (all of these patients recorded their blood pressure levels at home). However, five patients preferred pentolinium tartrate, since they obtained a more uniform reduction with the latter drug and also experienced fewer or less severe side-effects.

Comment

Clinically, mecamylamine behaved as a typical ganglion-blocking agent. Experimentally, the inhibition of sympathetic vasoconstrictor reflexes was less than had been observed previously with hexamethonium.[8] The reason for this discrepancy is not evident at present. The dosages of mecamylamine were smaller than those given in the hexamethonium studies. However, the doses of the two agents were approximately equipotent so far as hypotensive effects were concerned. It is possible that if the patients had been studied for longer intervals than from 30 to 60 minutes after mecamylamine a more complete inhibition of sympathetic vasoconstrictor reflexes would have been observed. Still, the reflexes remained active in three patients who were restudied during continuous oral administration of the drug. Finally, there is the possibility that mecamylamine in man has peripheral or central vasodilator effects in addition to its ganglion-blocking action. However, this supposition gains no support from the animal data § or from our own clinical observations.

Because of its potency, relatively long duration of action, and complete absorbability, the daily dose requirement of mecamylamine was far less than that of other ganglion-blocking drugs. It was hoped that the complete oral absorption of mecamylamine would obviate some of the difficulties entailed in the use of ganglionic blocking agents clinically. In the majority of the pa-

§ Stone, C. A.; Torchiana, M. L.; O'Neill, G. P., and Beyer, K. H.: Ganglionic Blocking Properties of 3-Methylaminoiso-Camphane Hydrochloride (Mecamylamine), a Secondary Amine, read before the American Society for Pharmacology and Experimental Therapy, Iowa City, Sept. 7, 1955.

tients the blood pressure response was more uniform from day to day than with pentolinium tartrate, but this was not always the case. In addition, such side-effects as constipation were just as prominent with the small completely absorbed doses of mecamylamine as with the relatively large poorly absorbed doses of other ganglion-blocking agents.

SUMMARY AND CONCLUSIONS

Mecamylamine seems to be completely absorbed from the intestinal tract of man. The hypotensive effect began after 1 hour, reached the lowest values at 2 hours and disappeared in 6 to 12 hours.

In equipotent hypotensive doses mecamylamine did not produce as marked an inhibition of sympathetic vasoconstrictor reflexes as had been observed previously with hexamethonium.

In 36 patients with severe hypertension treatment with mecamylamine in an average dose of 29 mg. per day was followed by a mean reduction in blood pressure of 21% systolic and 16% diastolic in the supine position and 27% systolic and 20% diastolic in the erect position.

Continuous treatment for one to four months frequently resulted in improvement in the optic fundi and occasionally in the electrocardiographic patterns. A decrease in blood urea nitrogen levels also was noted in most patients exhibiting slight elevations but not in those with marked nitrogen retention.

The side-effects were typical of those experienced with other ganglion-blocking agents.

In the majority of patients the development of "tolerance" was slight or nonexistent.

The addition of small doses of hydralazine appeared to produce a slight additional hypotensive effect in 3 of 13 patients. Reserpine seemed to produce an additional hypotensive effect in 5 of 11 patients.

Mecamylamine appears to offer a slight advantage over other ganglion-blocking agents in that the effective dose is much smaller, and with careful dosage regulation the blood pressure usually fluctuates less than with other blocking agents.

REFERENCES

1. Freis, E. D.; Finnerty, F. A., Jr.; Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension with Hexamethonium, Circulation **5**: 20, 1952.

2. Freis, E. D.; Partenope, E. A.; Lilienfield, L. S., and Rose, J. C.: A Clinical Appraisal of Pentapyrrolidinium (M & B 2050) in Hypertensive Patients, Circulation **9**:540, 1954.

3. Finnerty, F. A., Jr., and Freis, E. D.: Experimental and Clinical Evaluation in Man of Hexamethonium (C6), a New Ganglionic Blocking Agent, Circulation **2**:828, 1950.

4. Wilkins, R. W., and Culbertson, J. W.: The Effects of Surgical Sympathectomy upon Certain Vasopressor Responses in Hypertensive Patients, Tr. A. Am. Physicians **110**:195, 1947.

5. Freis, E. D.; Stanton, J. R.; Litter, J.; Culbertson, J. W.; Halperin, M. H.; Moister, F. C., and Wilkins, R. W.: The Hemodynamic Effects of Hypotensive Drugs in Man: II. Dihydroergocornine, J. Clin. Invest. **28**:1387, 1949.

6. Uprus, V.; Gaylor, J. B., and Carmichael, E. A.: Vasodilitation and Vasoconstriction in Response to Warming and Cooling of the Body: Criticism of Methods, Clin. Sc. **2**:301, 1936.

7. Bolton, B.; Carmichael, E. A., and Stürup, G.: Vasoconstriction Following Deep Inspiration, J. Physiol. **86**:83, 1936.

8. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Progress, Am. J. M. Sc. **197**:332, 1939.

9. Freis, E. D.: The Discrepancy Between Home and Office Recordings of Blood Pressure in Patients Under Treatment with Pentapyrrolidinium: Importance of Home Recordings in Adjusting Dosages, M. Ann. District of Columbia **28**:363, 1954.

10. Dustan, H. P.; Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Rheumatic and Febrile Syndrome During Prolonged Hydralazine Treatment, J. A. M. A. **154**:23, 1954.

A Rational Therapy of Systemic Lupus Erythematosus

N. B. KURNICK, M.D., Long Beach, Calif.

Our limited knowledge of systemic lupus erythematosus has restricted therapy to empirical and symptomatic approaches. Only corticotropin (ACTH) and the adrenal steroids have been generally accepted as valuable,[1] and it is doubtful that these influence the underlying disease.[2] Their benefit is probably due to their anti-inflammatory effect. It is the purpose of this paper to report a therapeutic regimen based upon observations [3] on the L. E.-cell phenomenon.[4]

Klemperer and co-workers [5] have reported that both the L. E.-cell bodies and the hematoxylin bodies found in tissues of patients with lupus contain depolymerized deoxyribonucleic acid (DNA). DNA occurs only in the chromosomes of cell nuclei and is thought to be the principal constituent of the gene, the carrier of hereditary characters. The breakdown of this molecule is probably not compatible with cell survival.

The L. E. cell, thus, represents a nucleolytic phenomenon. The depolymerized nuclear material may be sequestrated in the cytoplasm of the same cell or escape to be phagocytosed by another cell, to give the picture which Hargraves [6] described. Extracellular depolymerized nuclear masses ("globs" [6]) appear to be leucotactic, thus forming "rosettes." [7]

It appeared logical to suggest that the nuclear lysis is enzymatic.* Deoxyribonucleases (DNase), the enzymes which depolymerize DNA, are found in serum [9] and probably in all cells. Many bacteria produce DNase; the streptococcal product is known as "streptodornase."

The studies of my associates and me on the role of DNase in the L. E.-cell phenomenon led to the discovery that leucocytes contain an inhibitor of DNase.[3] The inhibitor was found to be a soluble protein with species specificity. When added to normal leucocytes simultaneously with lupus serum, the leucocyte extract containing the inhibitor of DNase prevents the L. E.-cell phenomenon.[3] It thus appears probable that the L. E.-cell phenomenon and the related tissue changes occur when the intracellular inhibitor is destroyed. This releases the intracellular DNase from control, with resultant lysis of the nucleus.

We have found that leukemic leucocytes are richer in inhibitor than mature leucocytes. This observation may have significance in the problem of cancer and senescence; e. g., cell death may ensue when the content of DNase inhibitor falls below a minimal protective level. It also explains the observed fact that leukemic blood, despite the greater ease in preparation of cell-rich smears, is a poor test object for the L. E.-cell phenomenon.

It was found possible to enhance the susceptibility of normal human leucocytes to

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From the Department of Medicine, University of California Medical Center, Los Angeles, and the Veterans Administration Hospital, Long Beach.

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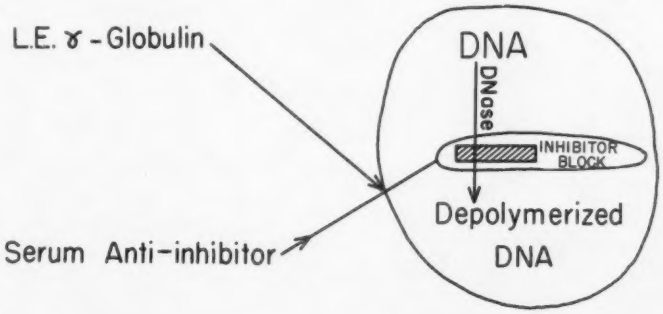
* References 5 and 8.

nucleolysis upon exposure to L. E. serum by washing the leucocytes with saline. This process was shown to remove some of their inhibitor.[3]

It remained to demonstrate the mechanism by which L. E. serum caused the destruction of intracellular inhibitor. We found that proteolytic enzymes [3] and both normal and L. E. sera were capable of destroying the extracted inhibitor upon incubation with it. Haserick and his associates [10] have shown that the γ-globulin from L. E. serum can elicit the L. E.-cell phenomenon when added to normal whole blood. However, this same γ-globulin factor has no influence upon the DNase inhibitor, nor does it induce the L. E.-cell phenomenon when added to washed leucocytes in the absence of serum.[11] Thus, the production of the nucleolysis which characterizes the L. E. cell requires cells, L. E. γ-globulin, and a factor present in both L. E. and normal serum which is capable of destroying the intracellular inhibitor.[11] The last factor appears to reside in Cohn's Fraction III. This fraction contains plasminogen, which in its active form (plasmin) is a proteolytic enzyme. It is possible that this proteolytic enzyme is the active principle which destroys the inhibitor. Plasminogen has been shown to become activated by clotting,[12] which may account for the enhancement of the L. E. cell phenomenon by clotting.[7]

Thus, the present status of our hypothesis of the pathogenesis of the L. E. cell may be summarized as shown in the Figure: Trauma to the cell in the presence of the L. E. γ-globulin (which may be an antibody against mesenchymal cell membranes) permits entry into the cell of the normal serum anti-inhibitor which destroys the intracellular inhibitor of DNase. Thus, the DNase is left free to produce the observed nucleolysis (depolymerization of DNA).

Our observations indicate that the DNase inhibitor can traverse the cell membrane in either direction.[8] The therapeutic application of the inhibitor appeared feasible, therefore. We found that the intramuscular, but not intravenous, injection of saline supernatants from leucocyte homogenates (which contain the DNase inhibitor) caused the depression of serum DNase activity for as long as 48 to 72 hours in rabbits. The same effect was produced in human subjects by the injection of whole blood intramuscularly from a compatible donor. It is thought that the effect in the latter experiment is due to the fact that intramuscularly infused leucocytes survive only briefly. Their wealth of DNase inhibitor is thus made available to the recipient. Furthermore, the stroma of the lysed leucocytes might be expected to serve a therapeutic purpose by adsorbing the circulating abnormal γ-globulin factor which is thought to be an antibody against mesenchymal cells.



In the past two years we have had the opportunity to apply this therapy to a small group of patients. Therapy consists of administering 30 ml. freshly drawn heparinized blood from a compatible donor intramuscularly three times weekly for several weeks,

then gradually reducing the frequency to once every 10 days. Recently we have substituted, in a few cases, concentrated suspensions of leucocytes in plasma, prepared by centrifugation of fresh whole normal or leukemic blood and stored frozen in single-dose vials (200,000,000 to 300,000,000 leucocytes in 1 to 5 ml/vial). The results were followed by observing the clinical course, reversal of L. E.-cell phenomenon, and reduction in serum DNase activity. Whereas the initial serum DNase activity is of no diagnostic significance,[8] its reduction during hemotherapy is a useful guide to the effectiveness of therapy.

We have found that DNase inhibitor solutions (prepared from leucocyte homogenates) may be sterilized by Seitz filtration and may be lyophilized. The dried powder must be stored at deep-freeze temperatures. It is possible, therefore, to prepare the partially purified inhibitor as a sterile concentrated solution, such that 1 or 2 ml. may be injected instead of 30 ml. with greater clinical convenience. One patient (Case 12) has been treated with such a preparation. The results are discussed below.

REPORTS OF CASES †

CASE 1.—A 39-year-old white woman developed a generalized erythematous eruption, fever, and arthralgias in the Spring of 1952. Skin biopsy was compatible with lupus erythematosus. Cortisone therapy produced incomplete remission. In spite of maintenance dosage up to 200 mg. daily, a severe exacerbation, lasting two months, occurred in October, 1952. In December, 1954, she developed a bullous eruption of the Senear-Usher type accompanied by albuminuria, azotemia, severe anemia, fever, and hypertension (blood pressure, 175/95). Hydrocortisone, 600 mg. daily, induced minimal improvement, severe Cushingoid state, and congestive failure. The L. E.-cell test was positive. Serum DNase was 30×10^{-4} units/ml. Hemotherapy was begun in January, 1955. Twenty-four hours after the first injection new vesicle formation had ceased, and the existing lesions healed rapidly during the next ten days. Since then, for the first time in three years, her skin has remained completely clear. Serum DNase activity was reduced to 17×10^{-4} units/ml. at the end of the first week and remained at approximately this level thereafter. Steroid therapy was gradually withdrawn over a period of one month. One week later, there was a relapse in symptoms, including pleuritis and pericarditis, which had been progressively improving. However, after 10 days, during which hemotherapy was the only treatment, sudden rapid improvement occurred. In the course of 10 days, the BUN dropped from 120 to 26 mg./100 ml., and in the course of 20 days the patient lost 38 lb. (17 kg.). Subjective and objective improvement were dramatic. Hypertension remained but responded well to hexamethonium and phenobarbital. Blood inoculations were continued but with decreased frequency; ultimately, 30 ml. every 10 days. When this dosage was instituted, she was asymptomatic except for slight stiffness in the knees for two or three days before her blood injections. After several weeks this complaint subsided, and she is now symptom-free and carrying on normal activities at home (September, 1955). She experienced an episode of coryza, bronchitis, second degree sunburn of the face, and an infected Bartholin's cyst without systemic reaction. The A/G ratio is 4.0:2.7 gm/100 ml. (as compared with 2.5:3 at the beginning of hemotherapy); the hemoglobin is 13 gm/100 ml. Intermittent albuminuria, pyuria, and bacilluria persist. BUN has not exceeded 30 mg/100 ml. for the past five months. The eosinophile count, which was 3 to 19/cu.mm. during steroid therapy rose to 150. All L. E.-cell tests have been negative since the institution of hemotherapy.

Summary.—This patient, with severe cortisone-resistant systemic lupus of three years' duration, has experienced a complete remission of seven months' duration while on hemotherapy. The marked improvement noted in this moribund uremic patient is unusual.

CASE 2.—A 12-year-old white girl noted the onset of illness in June, 1954, with malaise and weight loss, then chorea, stomatitis, tachycardia, and a diffuse painless red swelling of the left side of the neck. In November, 1954, sulfonamide therapy precipitated a typical butterfly eruption, pleural effusion, and nephropathy characterized by hypertension, facial edema, 4+ albuminuria, and "telescoped urinary sediment." An L. E.-cell test was positive. Cortisone therapy resulted in remission of symptoms, but elevation of the sedimentation rate, positive L. E.-cell tests, moderate anemia, thrombo-

† The following physicians referred these patients to us and/or cooperated in the therapy and follow-up: Drs. H. Perelson, M. Prinzmetal, R. Baum, E. L. Dubois, and S. Wiener, Los Angeles; R. W. Clapp and R. F. Peterson, Butte, Mont.; C. Waters, F. Waters, W. H. Olson, V. Maron, L. Meister, T. Lawrence, and J. R. Kimball, Long Beach, Calif. Drs. D. H. Hamm and W. C. Ralston gave advice in the preparation of the manuscript.

cytopenia, azotemia (BUN, 50 to 60 mg/100 ml.), hypertension, markedly abnormal urinary sediment, and pleural effusion persisted. In February, 1955, slight puffiness of the face, cardiac enlargement, and ulcerations of buccal and nasal mucosa were apparent in addition to the above findings. Serum DNase was 39×10^{-4} units/ml. Hemotherapy was begun with 20 ml. intramuscularly three times weekly, and cortisone was rapidly withdrawn. By the end of the second week, the L. E.-cell test was negative, serum DNase was reduced to 21×10^{-4} units/ml., mouth lesions were healed, hypertension had disappeared, and strength was increased. Urinalysis and BUN became normal. Blood injections were reduced to once weekly. Two weeks after the discontinuance of corticotropin, which was given for one week upon withdrawal of cortisone, a cutaneous and urinary relapse with fever occurred. Cortisone, 100 mg. daily, was added to the weekly hemotherapy. The cutaneous lesions cleared, but the urinary changes persisted and hypertension developed (blood pressure, 260/140). During the second week of this regimen, a cerebrovascular accident with right hemiplegia and sensory aphasia occurred. Prompt withdrawal of cortisone was again followed by a febrile cutaneous relapse and recurrence of L. E. cells. Hemoinnoculations were increased to three times weekly. After four days, the clinical evidence of lupus erythematosus activity subsided, urinary findings improved, and L. E.-cell tests again became negative. The hemiplegia and aphasia improved markedly in the course of two to three weeks. DNase determinations were unfortunately not done during the relapse, but they were 18 and 17×10^{-4} units/ml. one and two months later. After approximately two symptom-free months, there was a relapse characterized by rash, fever, hypertension, convulsions, elevation of BUN to 80 mg/100 ml., and positive L. E.-cell test. Hemotherapy was increased to once daily, with complete remission in one week. L. E.-cell tests became negative, and BUN fell to 22 mg. Since then, she has been maintained without evidence of L. E. activity on three blood inoculations weekly. However, she is hypertensive (blood pressure, 130-150/100-110) unless maintained on hexamethonium.

Summary.—A 12-year-old child with systemic lupus erythematosus and rapidly progressive renal damage despite cortisone therapy responded symptomatically to hemotherapy with disappearance of L. E. cells, azotemia, and urinary findings and reduction of serum DNase. After completion of steroid withdrawal, a relapse occurred. This subsided during the continuation of hemotherapy. A second relapse was aborted with increased frequency of blood inoculations.

CASE 3.—A 35-year-old white married woman developed a patchy vesicular and scaling erythematous dermatitis on the face, chest, arms, and thighs; multiple arthralgias; low-grade fever; malaise, and marked weakness in June, 1952. Sun bathing in August caused a severe exacerbation. A skin biopsy at that time was diagnosed as lupus erythematosus. She was treated with intramuscular gold for two months and then with quinacrine (Atabrine) for six weeks, with little if any improvement. Physical examination in May, 1953, revealed slight puffiness of the face; a few scattered papular, scaling, erythematous skin lesions; erythema of the palms and finger tips, and muscle tenderness. An L. E.-cell test was weakly positive. Serum DNase was 95×10^{-4} units/ml.

Hemotherapy was begun; after the fourth blood injection, she noted improvement in her skin lesions and myalgia and felt symptomatically improved. After three weeks of hemoinoculation therapy three times weekly the serum DNase was 29×10^{-4} units/ml. (48 hours after last injection) and L. E.-cell test was negative. The frequency of inoculation was reduced to once weekly. She continued to do well and was afebrile and essentially symptom-free. After 10 weeks of therapy her serum DNase was 55×10^{-4} units/ml. (11 days after last injection). Treatment was then discontinued for two months, at which time she noted return of weakness and had developed several skin lesions 1 cm. in diameter on forearms and upper lip. Serum DNase was 98×10^{-4} units/ml., and L. E.-cell test was again weakly positive. Hemoinoculation was reinstituted once weekly. After four injections she was again asymptomatic and the skin lesions were healing satisfactorily. Serum DNase seven days after the fourth injection of this series was reduced to 42×10^{-4} units and an L. E.-cell test was negative. She remained asymptomatic during the next four months of weekly injections. She was then referred to another physician upon my leaving that community. She failed to see him, and no follow-up is available.

Summary.—Remission of systemic lupus erythematosus of 1 year's duration occurred after 10 days of hemoinoculation therapy and was maintained during 8 months of hemoinoculation therapy, without adjunctive medication. A mild relapse after two months without therapy was again controlled within four weeks after resumption of injections at one- to two-week intervals. Serum DNase levels paralleled the clinical state: The level fell during therapy and rose during interruption of therapy.

CASE 4.—A 32-year-old married white woman experienced the onset of malaise and multiple arthralgias in April, 1954. At that time, a leucopenia was observed. She received cortisone for a brief period with remission. In December, 1954, she developed a generalized slightly pruritic erythematous eruption, intermittent fever (temperature to 101 F), arthralgias, and swelling of hands and ankles. The cutaneous eruption was intermittent and was purpuric on occasion. Family history revealed that a brother had died at the age of 20 from systemic lupus with renal involvement. In February, 1955, a strongly positive L. E.-cell test was obtained. She was treated with intravenous corticotropin for five days and then with hydrocortisone, 160 mg. daily. The arthralgias and fever promptly subsided, but dermatitis and buccal lesions continued to recur, and L. E.-cell test remained moderately positive. Serum albumin was 3.4 gm. and globulin, 3.8 gm/100 ml. Urine was normal. Serum DNase was 46×10^{-4} units/ml. She was started on 30 ml. fresh blood intramuscularly three times weekly. By the evening of the first injection her skin lesions had cleared, and they have remained absent except for a very mild eruption noted in the morning and clearing by afternoon during the second week of therapy. She has been completely asymptomatic and has had no skin lesions since early March. By the end of March her hydrocortisone dosage had been reduced to 30 mg. daily, and by the end of June, to 5 mg., and it was then eliminated. An L. E.-cell preparation after four weeks of blood injections was negative; serum DNase was 37×10^{-4} units. Injections were reduced to 30 ml. twice weekly. After eight weeks of blood treatment, an L. E.-cell test was again negative; serum DNase was 21×10^{-4} units/ml. Urinalysis and hematological examinations have given normal results.

Summary.—In a 32-year-old woman systemic lupus of one year's duration was well controlled except for recurrent erythematous "urticarial" skin lesions and buccal ulcerations on 160 mg. cortisone daily for two weeks. With institution of blood therapy and gradual reduction of cortisone to 20 mg. daily she rapidly became completely asymptomatic. Serum DNase, normal initially, fell approximately 50% during hemoinoculation therapy.

CASE 5.—A 21-year-old white married woman noted swelling, tenderness, and redness of fingers, wrists, elbows, and knees in December, 1953, followed by fever and pleuritis. She was treated with 50 mg. cortisone daily with subsidence of pleuritis in about two months but with persistence of joint pains and progressive increase in muscle aches and abdominal pain. Despite continued cortisone therapy she suffered recurrence of fever and pleuritis in December, 1954, and developed an erythematous rash on cheeks and V-area of neck. The abnormal physical findings included 2 to 3 cm. tender red nodules in the scalp, erythematous eruption in the butterfly area, eroded lesions on buccal mucosa, pulmonic systolic murmur, and a pleural and pericardial friction rub. Cortisone was replaced with 40 units of corticotropin-gel intramuscularly three times daily for six weeks, without significant improvement. L. E.-tests were repeatedly strongly positive. Urinalyses were negative. Erythrocyte sedimentation rate was 40 mm. in an hour. Serum DNase was 67×10^{-4} units/ml. Corticotropin was discontinued on March 1, 1955. Intramuscular blood inoculations were instituted on March 7, 1955, and continued three times weekly for two months, then twice weekly for two weeks, then once weekly until June 10, 1955, when they were increased to twice weekly again. During the 24 hours following the first blood inoculation the patient's temperature rose to 102 F; there was exacerbation of joint, muscle, and skin symptoms and periorbital edema. These symptoms improved during the next 48 hours. Subsequent blood injections were uneventful. She became afebrile after one week and remained afebrile thereafter. Pleuritis and pericarditis disappeared. At the end of the first week of blood therapy DNase was 42×10^{-4} units/ml. and the L. E.-cell preparation was weakly positive; one week later DNase was 30×10^{-4} units/ml. and the L. E-cell test was moderately positive. The DNase remained at approximately the same level until the blood injections were reduced to once weekly, and the L. E-cell tests became negative after five weeks of therapy. The skin lesions began to improve after the first week and were absent after the second week. The arthralgias and myalgias showed no significant change for approximately one month; they then subsided coincidentally with the disappearance of the L. E. cells, and they have continued to be minimal.

In late May, one week after the hemoinoculations had been reduced to once weekly (i. e., the day before the next hemoinoculation), serum DNase was 82×10^{-4} units/ml. and an L. E.-cell preparation was negative. Seven days after the second weekly blood injection the L. E.-cell test was moderately positive. Clinically the patient continued to do well except for some scalp tenderness and slight discomfort in her thighs. However, the relapse in serum DNase level and L. E.-cell test caused us to increase the frequency of injections to twice weekly. One week later, serum DNase was 37×10^{-4} units/ml. and the L. E.-cell test was very weakly positive. She was again asymptomatic and appeared clinically well. One week later the L. E.-cell test was negative, DNase was 30×10^{-4} units/ml., and

erythrocyte sedimentation rate was 10 mm. in an hour.

Summary.—A 21-year-old patient with systemic lupus of one and one-half years' duration, inadequately controlled by cortisone, experienced relief from fever, myalgias, arthralgias, pericarditis, pleuritis, and cutaneous lesions within five weeks after institution of hemotherapy. Serum DNase activity was reduced after one week, and the L. E.-cell test became negative after five weeks. However, DNase activity rose and the L. E.-cell test became positive when blood injections were reduced to once weekly. The rise in DNase preceded the return of L. E. cells. These abnormalities were not associated with clinical relapse during the three weeks she was on this regimen. Blood inoculations were then resumed twice weekly, with return to normal in the blood findings.

CASE 6.—A 32-year-old Negro woman, seen in June, 1953, complained of malaise, arthralgias, occasional swelling of joints, myalgias, and low-grade fever of approximately two years' duration. Laboratory data revealed slight anemia, leucopenia, a positive L. E.-cell test, and serum DNase 80×10^{-4} units/ml. Intramuscular hemoinoculation, 30 ml. three times weekly, was instituted. At the end of the first week, L. E.-cell test was negative, DNase was 40×10^{-4} units/ml., and the patient was subjectively improved. After three weeks, she was asymptomatic, L. E.-cell test remained negative, and serum DNase fluctuated between 30 and 40×10^{-4} units/ml. After one month, the frequency of injection was reduced to twice weekly, and two weeks later, to once weekly. She continued to be seen for four months, during which complete remission persisted.

Summary.—A 32-year-old Negro woman who had suffered from systemic lupus erythematosus for two years responded to hemoinoculation therapy with rapid subsidence of symptoms, disappearance of L. E. cells, and reduction of serum DNase activity.

CASE 7.—A 52-year-old white married woman had complained of pain and swelling of knees, shoulders, wrists, elbows, and fingers; temperature to 102-103 F; bouts of severe pleuritic pain; marked lassitude, and congestive heart failure for one and one-half years when first seen in June, 1954. A diagnosis of systemic lupus erythematosus had been made about one year before I saw her, and she was treated with 80 to 100 mg. of cortisone daily, with improvement. However, she continued to experience brief febrile episodes associated with severe pleuritic pain. Physical examination revealed generalized muscular tenderness, slow painful motions, and moderate swelling of both knees. There was a soft apical systolic murmur, a few basal rales, and 3+ edema of the ankles. The liver was palpable 2 cm. below the costal margin. Urinalysis showed 1+ albumin, trace of glucose, 2 to 5 WBC per high-power field. Serum DNase was 88×10^{-4} units/ml., and the L. E.-cell test revealed a few typical L. E. cells. BUN was 21 mg/100 ml.; serum albumin and globulin were 2.8 and 3.4 gm/100 ml., respectively. She was treated with gradual reduction in cortisone over a two-week period, while corticotropin-gel was introduced. The corticotropin was started at 40 units per day and reduced at the rate of 2.5 units per day. There was improvement in the congestive failure and in symptoms. When corticotropin had been reduced to 20 units per day the patient developed fever (temperature to 101.4 F), severe left chest pain aggravated by breathing and coughing, and swelling of both knees. A left pleural friction rub was heard. L. E.-cell test was strongly positive. Treatment with intramuscular blood, 30 ml. three times weekly, was instituted. Within 24 hours her fever, arthralgia, and pleuritis improved. After one week of blood therapy, during which corticotropin was eliminated, serum DNase was 35×10^{-4} units/ml. She was continued on hemotherapy three times weekly for two months, during which period she was asymptomatic except for slight stiffness of the knees in the evenings. L. E.-cell test became negative. At the end of this period she was referred to a physician in another city. She has been maintained on salicylates alone for the past eight months. Her course has been similar to that on cortisone before blood therapy was instituted, characterized by moderate arthralgia and myalgia and episodes of fever and pleuritic pain.

Summary.—In a 52-year-old white woman arthralgias and pleuritis due to systemic lupus of one and one-half years' duration responded to hemotherapy, with symptomatic improvement, disappearance of L. E. cells, and reduction in serum DNase. On cortisone and salicylate therapy control was less satisfactory.

CASE 8.—A 16-year-old white girl complained of severe pain in arms, fingers, and neck since the Fall of 1953. An L. E.-cell test was positive in December, 1953. Cortisone was given, 150 mg. p. o. daily, with only slight improvement in her symptoms. The dosage of cortisone was gradually increased. During most of 1954 she was maintained on 250 to 300 mg. cortisone daily, but even on this regimen she was not free of pain. Characteristic Cushingoid changes developed. Repeated L. E.-cell tests remained

strongly positive. A serum sample examined by us on Feb. 14, 1955, revealed a very strongly positive L. E.-cell test and 31×10^{-4} units DNase per milliliter. In the middle of March, 1955, she was started on 25 ml. fresh heparinized compatible blood intramuscularly three times weekly. Her cortisone dosage was reduced to 150 mg. daily, and she was then switched to prednisone (Meticorten), 40 mg. daily. This was reduced to 25 mg. daily during the fourth week of blood therapy. Symptomatically she was considerably improved during this period, but when the prednisone was reduced below 25 mg. daily she again developed muscle and joint pains and occasional slight fever. At the end of two weeks of hemoinoculation treatment her leucocyte count was 3900 and sedimentation rate 51 mm. in an hour and there were still moderate numbers of L. E. cells found. A serum DNase test at the end of four weeks of intramuscular blood therapy was 10×10^{-4} units/ml. In June, 1955, hemotherapy was discontinued. In order to control the myalgias, she has required 160 mg. cortisone and 40 mg. prednisone daily. L. E.-cell tests remain positive, and the Cushing syndrome persists.

Summary.—A 16-year-old girl experienced only fair control of her arthralgias while maintained for 15 months on 250 to 300 mg. cortisone daily. L. E.-cell tests were persistently strongly positive. Symptomatic improvement and moderate reduction in corticoid therapy was achieved with hemoinoculation, but symptoms recurred on further reduction of corticoids.

CASE 9.—A 24-year-old white woman, seen in January, 1955, had complained of multiple arthralgias and myalgias and tenosynovitis of flexor tendons of fingers with temporary flexion contractures for four years. Shortly after the onset of her illness, heliotherapy was followed by fever and posterior cervical adenopathy, with redness and tenderness of the nodes. Sternal marrow and peripheral blood revealed L. E. cells. Corticotropin and cortisone therapy were followed by marked improvement and moderate Cushingoid state, but she continued to experience intermittent bouts of joint pain, tender nodules in calf muscles and scalp, erythema and tenderness of finger tips, and low-grade fever. In November, 1953, she had an acute episode of pleuritis. In September, 1954, upon reduction of her maintenance cortisone dose from 50 to 25 mg., she suffered severe exacerbation of the pleuritic pain, joint and muscle symptoms, fatigue, and fever. Pleural and pericardial friction rubs, butterfly erythema, and temperature of 103 F were noted. These complaints increased for several weeks despite rapid increase in cortisone to 400 mg. intramuscularly daily and institution of corticotropin, hydrocortisone 600 mg. daily, and chloroquine. Her symptoms gradually subsided over the course of the next two months, during which she was maintained on 400 mg. of hydrocortisone daily. Severe Cushingoid changes developed. At this time (January, 1955) a peripheral blood L. E.-cell test was weakly positive and serum DNase was 110×10^{-4} units/ml.; the albumin globulin ratio was 2.4 : 4.8; γ-globulin, 1.8 gm/100 ml. During the next three weeks hydrocortisone was gradually reduced to 260 mg. daily, with exacerbation of malaise, weakness, pleuritic pain, and slight fever (temperature to 100 F). An L. E.-cell test was strongly positive. Intramuscular administration of blood was begun (30 ml. three times weekly). By the end of the first week of this regimen, hydrocortisone therapy was reduced to 100 mg. daily and corticotropin-gel was begun (40 mg. daily), At this time, the L. E.-cell test was negative and DNase was 65×10^{-4} units/ml. Her symptoms subsided to approximately the status which had been attained in January, 1955, when she was receiving 400 mg. hydrocortisone daily. Hydrocortisone was reduced further at the rate of 10 mg. daily until a dose of 20 mg. daily was reached. There was no loss in weight or change in Cushingoid appearance during this period, although blood pressure fell to normal, the 17-ketosteroid excretion fell from 21 to 8.0 mg./24 hours and the patient's affect became calmer and sleep was normal. During the course of the next two weeks, hydrocortisone was very gradually reduced to 5 mg. daily and corticotropin, to 20 units daily. On this regimen the patient complained of weakness and somnolence and noted slight exacerbation of chest pain and transitory swelling of interphalangeal joints. Blood pressure was 90/60 and 17-ketosteroid excretion was 3.5 mg. in 24 hours; eosinophile count, 110/cu. mm.; serum protein, 7.2 gm.; albumin, 3.3 gm., and globulin, 3.9 gm/100 ml. Corticotropin was increased to 20 units b. i. d., and hydrocortisone therapy was stopped. On this regimen the symptoms improved again but did not disappear; blood pressure rose to 130/86, and 17-ketosteroid excretion rose to 6.5 mg.; eosinophile count fell to 66/cu. mm. When corticotropin dosage was again reduced to 12.5 units b. i. d., pain and intermittent swelling of interphalangeal, wrist, and elbow joints (with flexion deformity of the latter) and chest pain became aggravated. Ketosteroid excretion varied between 3 and 4 mg. in 24 hours, and eosinophile count was 140/cu. mm. Prompt remission followed increase of the corticotropin dosage to 40 units b. i. d. for three days, but exacerbation of symptoms again occurred when the dosage was reduced to 12.5 units b. i. d. Throughout, L. E.-cell preparations were negative and serum DNase remained at lower levels than initially. Since the patient could not tolerate reduction of steroid therapy, because of joint pains and recurrence of flexion

deformity of the right elbow, prednisone, 10 mg., was given and corticotropin and hemotherapy were stopped. Within several hours there was improvement in symptoms, and on 20 to 30 mg. of prednisone daily a fairly good remission has been maintained. L. E. cells are reported to continue to be absent two months after discontinuance of the two-and-one-half month course of hemotherapy three times weekly. Her clinical condition resembles the state maintained previously on 400 mg. hydrocortisone daily. The Cushingoid appearance persists two months after the institution of prednisone.

Summary.—A 24-year-old woman with systemic lupus of four years' duration had several mild and one severe exacerbation while under treatment with steroids. The latter exacerbation subsided during therapy with very large doses of hydrocortisone (400-600 mg. daily) and recurred when dosage was cut to 260 mg. daily. During hemotherapy, satisfactory but incomplete clinical remission was maintained on 40 units of corticotropin-gel daily without corticoids. L. E. cells disappeared, and serum DNase fell. Although these changes were maintained, further reduction in corticotropin dosage was associated with relapse in myalgias and arthralgias. It appears probable from the findings of hypotension, low 17-ketosteroid excretion, increased eosinophile counts, and rapid response to large doses of corticotropin or small doses of steroids that this patient's exacerbation when steroid therapy was reduced was due to hypoadrenocorticism secondary to four years of corticoid administration.

CASE 10.—An 18-year-old white single woman noted swelling of the feet and ankles and puffiness of the eyes in the Spring of 1953. A diagnosis of systemic lupus erythematosus was made, and she was treated with cortisone. Since the Summer of 1953 she had noted a rash on her face and arms which was aggravated by exposure to sunlight. She also complained of recurrent pain and swelling of elbows, wrists, and knees. Since the Summer of 1954 she had experienced frequent attacks of pleuritic pain. Laboratory examinations in April, 1954, revealed slight anemia, elevated sedimentation rate, positive L. E.-cell tests, albuminuria (3+), and abnormal urinary sediment. Serum albumin was 2.7 gm.; globulin, 4.2 gm/100 ml. In the Winter of 1955 she noted rapid progression of swelling of her ankles, legs, abdomen, and face and severe pleuritic chest pain. In March, 1955, blood pressure was 160/100; urinalysis revealed 3+ albumin, 20 to 30 WBC, 120 to 150 RBC, 10 to 20 hyaline casts, and 3 to 5 granular casts per high-power field. Moderate anemia and a normal white blood cell count were noted. Blood NPN was 120 mg/100 ml.; creatinine, 7 mg/100 ml.; serum albumin, 1.7 gm., and serum globulin, 3.0 gm/100 ml. An L. E.-cell test was strongly positive. Cortisone was continued at 160 mg. daily. On March 19, 1955, she received 30 ml. of fresh heparinized blood intramuscularly, and this was given three times weekly thereafter. On that day an L. E.-cell test was strongly positive and serum DNase was 12×10^{-4} units/ml. Her rash cleared and the chest pain improved considerably during the first week of hemotherapy. On the sixth day of blood therapy she had several convulsions and lapsed into a uremic stupor, from which she never recovered. Cortisone was discontinued, and hemoinoculation was continued. She remained afebrile, and L. E.-cell tests were negative. Bloody gastric fluid was obtained on gastric suction, and the stools became tarry. She died on April 13, 1955.

At postmortem examination ‡ moon-shaped Cushingoid facies was noted and hands, vulva, legs, and ankles were edematous. There were fibrinous pericarditis, edema of the lungs, and 1100 cc. of ascitic fluid. The adrenal cortices were much diminished in thickness. The myocardium showed focal areas of interstitial fibrinoid degeneration, with infiltration of plasma cells and lymphocytes. Periarterial fibrosis was noted about the central arteries of the spleen. The kidneys, which weighed 510 gm. together, had smooth surfaces with occasional petechial hemorrhages and revealed severe endothelial proliferation in the glomerular capillaries and focal necrosis of the glomerular tufts. The basement membranes showed thickening and hyalinization. Most glomeruli were atrophic and hyalinized. The interstitial tissue contained many foci of lymphocytes. The bone marrow showed depression of erythropoiesis.

Summary.—An 18-year-old woman with systemic lupus of two years' duration presented with anasarca, azotemia, a skin rash, and pleuritis, despite maintenance steroid therapy (160 mg. cortisone daily). The latter two symptoms responded upon the addition of hemoinoculation to the steroid therapy, but she lapsed into uremic coma within a week and died three weeks later. Necropsy revealed changes consistent with systemic

‡ Performed by Dr. J. A. Tuta, Seaside Hospital, Long Beach.

lupus erythematosus and uremia, including severe glomerulonephritis.

CASE 11.—A 17-year-old white girl noted in November, 1954, the onset of pain and weakness in legs and wrists and in February, 1955, a severe exacerbation with pleuritis, pericarditis, chills, fever (temperature of 105 F), and petechial eruption on the legs. Pericardial and pleural friction rubs, cardiomegaly (probable pericardial effusion), and congestive failure were noted. There was rapid improvement following the administration of corticotropin, cortisone, digitalis, and mercurial diuretics. After two months steroids were discontinued. In May, 1955, she developed nocturia, frequency of urination, migratory polyarthritis, and temperature of 102.5 F. In July, 1955, she developed a vesicular and bullous eruption on her face, nausea, and vomiting. Physical examination on Aug. 11, 1955, revealed an acutely ill febrile woman with severe cutaneous and muscular hyperesthesia, bullous eruption of face, ulceration of nasal and buccal mucosa, cardiomegaly, loud basal systolic murmur, and tachycardia; B. P. was 122/64. Laboratory data revealed strongly positive L. E.-cell test, 2.0 gm. albumin and 3.9 gm. globulin per 100 ml. of blood, moderate anemia and leucopenia (3500 WBC/cu. mm.), 2+ albuminuria, 3 to 5 WBC and 100 to 150 RBC per high-power field, and a moderate number of coarsely granular casts. BUN was 66 mg/100 ml. Serum DNase activity was 157×10^{-4} units/ml. Electrocardiogram showed changes suggestive of myocardial damage. On Aug. 13 purulent left otitis externa developed. The next day the patient had diffuse pyodermia of the face, bilateral otitis, and severe ulceration of the mouth. On Aug. 15 hemotherapy three times weekly was instituted. The pyodermia continued to exacerbate, and on Aug. 17 the temperature rose to 103.5 F. One dose of a sulfonamide followed by three days of chloramphenicol therapy resulted in reduction of fever and clearing of the pyodermia. Thereafter, she was free of skin lesions and her mouth healed. However, she continued to run a fever (temperature up to 101 F). After two weeks of hemotherapy a right pleural friction rub was noted and the leucocyte count rose to 15,000/cu. mm., with a shift to the left in the granulocyte series. She was treated with penicillin and streptomycin. After three weeks of hemotherapy she appeared clinically improved, in that temperature was lower, myalgia and hyperthesia were less, and skin and mucosa were clear. However, there was moderate ascites and edema of dorsum of feet. The congestive failure did not respond to digitalis. L. E. preparations on the 2d, 10th, 16th, and 22d days of hemotherapy were positive. Serum DNase was reduced to 2×10^{-4} on the 2d day, 3×10^{-4} on the 10th, and 22×10^{-4} on the 22d from the original level of 157×10^{-4}. The patient died on the 27th day of therapy.

Postmortem examination § revealed fibrinous pleuritis, obliteration of the pericardial space, a necrotizing myocarditis (but no endocarditis), and cloudy ascitic and joint fluid. The kidneys were pale and swollen, with several small hemorrhagic areas.

Summary.—A 17-year-old girl with acute systemic lupus for one year presented in acute exacerbation with myocardial, pericardial, pleural, and renal involvement. She died within four weeks after hemotherapy was instituted, apparently of myocardial disease and diffuse serositis due to acute systemic lupus. Hemotherapy resulted in reduction of serum DNase activity but did not reverse the positive L. E.-cell test.

CASE 12.—A 37-year-old Negro man had experienced multiple arthralgias and joint swelling since the Summer of 1952. There were associated intermittent fever, hyperpigmentation of the skin in the butterfly area and chest, slight dyspnea, and nonproductive cough. In October, 1952, L. E. cells were found. He received intravenous corticotropin in October, 1952, and May, 1953, with improvement on both occasions. In February, 1954, a lung biopsy revealed pulmonary fibrosis and emphysema. No hematoxylin bodies [5] were seen. He was readmitted on Feb. 10, 1955, because of persistence of his joint pains and swelling, low-grade fever, and axillary dermatitis. On Feb. 25, 1955, he was started on 2 ml. three times weekly of Seitz-filtered saline extract (containing 1:1000 thimerosal) of ultrasonically disrupted washed leucocytes obtained by centrifugation of bank blood (one to four weeks old; each milliliter of extract was approximately equivalent to 10 ml. of whole blood; this solution was shown to contain the DNase inhibitor [8]; it was stored frozen). No effort to provide compatible blood was made, since the leucocytes were relatively freed of red blood cells and plasma by repeated centrifugation and saline washing before disruption. After one month of this therapy there was improvement in arthralgias; the swelling of the wrists subsided and freedom of motion was greatly improved. The shoulders and knees remained painful, and the axillary dermatitis persisted. He was afebrile. At the end of six weeks of this therapy, with no further improvement, he was started on 2 ml. three times weekly of a suspension of the leucocyte sediment obtained in preparation of the DNase inhibitor initially ad-

§ Performed by Dr. D. B. Lee, Seaside Hospital, Long Beach.

ministered (containing 1:1000 thimerosal; 1 ml. suspension equivalent to 10 ml. whole blood; this suspension contains no DNase inhibitor[3]). This was given for one month, with continued gradual improvement. On May 16, 1955, he was started on 2 ml. of a suspension of whole leucocytes, three times weekly. It was prepared similarly to the preceding preparations but not filtered. It also was frozen for storage with thimerosal added. On this regimen he became relatively comfortable but had occasional pain in shoulders and thighs. DNase levels varied from 22 to 80×10^{-4} units/ml.; L. E.-cell tests varied from negative to moderately positive during treatment; the two changed in parallel. In the middle of June all therapy was withdrawn. At that time, the serum DNase was 36×10^{-4} units/ml.; L. E.-cell test was negative. Progressive increase in arthralgia, pulmonary infiltration, cough, axillary and anal pruritus, and weight loss were not influenced by treatment with quinine during the first three weeks of August. The L. E.-cell test became positive, and serum DNase rose to 92×10^{-4} units/ml. He was then started on hemotherapy three times weekly. After two weeks he noted slight improvement in the arthralgias and clearing of the axillary dermatitis. Serum DNase was 60×10^{-4} units/ml., and the L. E.-cell test was negative. At this writing he has received four weeks of hemotherapy. His skin is clear, and the only joints which are still symptomatic are wrists and fingers.

Summary.—In a 37-year-old Negro man known systemic lupus of two and one-half years' duration had run a relatively mild course characterized primarily by arthritis and mild pulmonary fibrosis. The patient was treated with fractions of leucocytes isolated from bank blood. An undramatic gradual improvement occurred, slightly more marked during treatment with the sediment, which contains no inhibitor of DNase, than during the preceding period with inhibitor. The possible significance of this observation is considered below. It may be remarked here that the storage of blood and the washing of leucocytes results in considerable loss of inhibitor,[3] although the leucocyte homogenate supernatant did demonstrate moderate DNase inhibition on in vitro testing by the methyl green method.[9] L. E.-cell tests and DNase levels varied together but did not reveal a consistent trend. The exacerbation of symptoms which followed discontinuance of therapy appeared to be reversed by hemotherapy.

COMMENT ON CLINICAL MATERIAL

The results of hemoinoculation therapy in 11 patients may be summarized as good in 7 (Cases 1 to 7), doubtful in 2 (Cases 8 and 9), and poor in 2 (Cases 10 and 11). Of the poor results, one (Case 10) was in a patient who was uremic when therapy was begun and died in less than four weeks in uremic coma. Clinically there was, however, subsidence of fever, pleuritis, and cutaneous rash and disappearance of L. E. cells. The other failure (Case 11) terminated fatally within four weeks with evidence of persistently active disease. The two doubtful results occurred in patients who had been on high dosages of corticoids for long periods and who improved during blood therapy and considerable reduction in steroid dosage but who suffered recurrence of myalgias and arthralgias upon further reduction in steroid therapy. Two other patients (Cases 1 and 2) listed as "good" also had similar experiences; but, in both of these, discontinuance of steroid therapy was persisted in and remissions occurred with continuance of hemoinoculation therapy alone in four days and two weeks, respectively.

Soon after the institution of hemotherapy, circulating serum DNase activity was reduced in all patients. This enzyme activity tends to be increased in systemic lupus erythematosus.[8] We consider the response of the serum DNase to be a useful guide to the effect of therapy and to the indicated frequency of injections. Thus, the reduction in DNase tended to precede the disappearance of L. E. cells; and, as in Case 5, the return of serum DNase to higher levels when the frequency of hemoinoculations was reduced preceded the reappearance of the L. E.-cell phenomenon. When the frequency of injection was increased, obvious symptomatic improvement ensued.

Other changes which were noted in our patients soon after the institution of hemotherapy were clearing of cutaneous eruptions (usually in the first week); subsidence of fever; improvement in arthralgias, myalgias, malaise, fatigability, serositis, and urinary

findings, and disappearance of the L. E.-cell phenomenon (three to six weeks). The leucocyte count did not appear to be altered. The erythrocyte sedimentation rate remained elevated in most patients. This persistent elevation may be due to the breakdown of protein in the injected fluid.

Our series of patients in whom blood inoculation was followed by improvement includes one (Case 1) who was considered to be moribund from severe cutaneous, renal, and serosal involvement which had failed to improve on 600 mg. of hydrocortisone daily. The disease in three others (Cases 4, 8, and 9) was only partially controlled by very high doses of steroids and improved with hemoinoculation and reduction of steroid dosage to relatively low level.

The experience with the patients who had received corticoids for some time before institution of hemoinoculation suggests that the exacerbations noted on discontinuance of the steroids may be due to hypoadrenocorticism induced by the steroid therapy.[13] The subnormal response of Case 9 to corticotropin, as indicated by the absence of response in circulating eosinophiles and urinary steroid excretion, is indicative of this state. Myalgias, arthralgias, and flexion deformities may occur in primary hypoadrenocorticism [14] and the hypocorticism of cortisone withdrawal.[13] However, at least in Case 2, it appears that the symptoms must be attributed to relapse of the basic disease. This, too, may be a consequence of the hypoadrenocorticism, resembling the systemic exacerbations observed in patients with rheumatoid arthritis following the withdrawal of corticoids: Slocumb [13] has described fatigability, aching of joints and muscles, emotional instability, fever, pericarditis, pleuritis, pulmonary consolidation, renal irritation, and even positive L. E.-cell test. The symptoms usually developed only when the dosage had been reduced to approximately that used in the treatment of adrenal insufficiency (20 to 30 mg. cortisone daily). These symptoms persisted a few days to a week or more in Slocumb's patients and subsided spontaneously despite further reduction and elimination of cortisone (cf. Cases 1 and 2) or upon slight increase in dose (cf. Case 9) followed by more gradual reduction.

Beneficial results were noted in patients receiving hemotherapy during the continuation of cortisone therapy, as evidenced by clearing of signs and symptoms not previously controlled and by the maintenance of improvement on greatly reduced dosage (Cases 1, 2, 4, 8, and 9 prior to reduction in dosage below 20 to 30 mg. daily). This suggests that the combination of hemotherapy and steroids may be useful in many patients by permitting adequate control on greatly reduced steroid dosage, even if its complete withdrawal is not feasible. However, the possibility that steroids inhibit somewhat the maximum effect of hemoinoculation must also be entertained, since steroids may inhibit the destruction of the inoculated leucocytes.

It is improbable that the infused blood acts by inducing adrenocortical stimulation by a "protein shock" mechanism. Several of the patients (notably Cases 1, 2, 4, and 5) responded much more markedly to the hemoinoculation treatment than they had to large doses of steroids. Also, eosinopenia was not produced by the injections, nor was there any increase in 17 ketosteroid excretion. In Case 9 subnormal levels of 17 ketosteroid excretion, rise in eosinophile count, and fall in blood pressure were not prevented by the blood injections when the steroid dosage was greatly reduced. In Case 1 rise in eosinophile count was noted following corticotropin withdrawal during continued hemoinoculation therapy.

The procedure appears to be quite safe. In one patient (Case 5) a brief febrile episode may have been precipitated by the first blood inoculation. Dr. J. Colsky, of Maimonides Hospital, Brooklyn, reported a similar experience to us. A patient with systemic lupus, not otherwise treated, was given 5 ml. intramuscularly of buffy coat obtained from a leukemic patient. Within 24 hours there was fever (temperature of 103 F), a butterfly

eruption (not previously present), myalgia, and arthralgia; immature leucocytes were observed in the peripheral blood. The episode subsided in 48 hours. A second injection was then given without event. At the end of a week, the patient was asymptomatic, and L. E. cells were no longer apparent. Without further therapy she has remained in remission for approximately one year.

We prefer to use compatible blood in order to avoid the possibility of major blood-group sensitization during prolonged therapy.

It is possible that autohemoinoculation may be equally beneficial. However, I have not investigated this possibility, and I suspect that it would not be as useful. The infused leucocytes would probably not be destroyed, and if they were destroyed they might well be poor in DNase inhibitor because of their exposure to the abnormal L. E. factor during circulation prior to inoculation.

It may be noted that hemotherapy (usually in the form of autohemotherapy) has been advocated in the past for the treatment of dermatoses and arthritides, psychoses, and other states.[18] It is our feeling that the clinicians with whom this empiric therapy found vogue noted its value in some of their patients, namely, those with systemic lupus, even though it was not recognized as such. Since the classification was ill-defined, the therapy became applied to a large variety of disease states which had in common only eruptions or joint pains or resistance to conventional therapies. Failure in the vast majority of these caused the therapy, always lacking in scientific basis, to fall into ill-repute. Also, as *post hoc* rationales were introduced and immunologic mechanisms were suggested, the therapy was modified to serotherapy. The cellular elements were discarded. If our hypothesis is correct, the inefficacy of hemotherapy was thus assured.

The therapeutic effects of some other regimens in systemic lupus erythematosus may also be explained on the basis of the mechanism of cell destruction we have adduced for systemic lupus and which provides the rationale for hemotherapy (i. e., the mechanism of the L. E.-cell phenomenon secondary to destruction of the DNase inhibitor described in the introduction). The adrenal steroids, which alone are generally considered valuable,‡ may have their beneficial effect (1) by inhibiting the production of the abnormal γ-globulin factor[10]; (2) by preventing the reaction of the abnormal γ-globulin with the mesenchymal cell surface; (3) by their lymphoclastic action, causing the release of DNase inhibitor, which is abundant in lymphocytes,[3] and/or (4) by diminishing the inflammatory reaction in the surrounding tissue to cell destruction. We believe that the last hypothesis of corticoid action is the most probable. This would account for the progression of the disease, though at a slower pace, during steroid therapy, since cell destruction proceeds. Quinacrine is frequently valuable in the therapy of discoid lupus.[15] It has been reported to be both beneficial[16] and deleterious[15] in systemic lupus. We have found that quinacrine combines firmly with polymerized DNA in vitro and thereby renders it insusceptible to attack by DNase.[19] This fact accounts for the inhibitory effect of quinacrine on the L. E. cell phenomenon in vitro.[16] The mechanism is quite different from that of the intracellular DNase inhibitor, which acts upon the enzyme and not upon the substrate,[3] as does the antimalarial. It is doubtful, however, that the latter mechanism is advantageous, since the combination of the drug with the nucleic acid probably interferes with the physiological function of the nucleus. Chloroquine has also been reported to be useful in the treatment of discoid[17] and perhaps of systemic lupus.[16] This drug, I have found, also combines with DNA and thereby prevents its depolymerization. However, much higher concentration of chloroquine than of quinacrine is required for this effect.[19] This is consistent with Dubois'[16] observation that approximately four times the concentration of

‡ References 1 and 2.

chloroquine as of quinacrine is required to prevent the L. E.-cell phenomenon in vitro.

The interpretation of the results in Patient 12, who was treated with the leucocyte fractions, is complicated by several factors. In the first place, bank blood rather than fresh blood was used. The storage of blood results in considerable loss of DNase inhibitor, which is not stable for long periods at 4 C. Secondly, the washing of the leucocytes during their isolation results in considerable loss of DNase inhibitor.[3] Indeed, the preparations were shown, in vitro, to be only moderately potent DNase inhibitors, and different batches varied in their activity. This may account for the irregularity of the serum DNase and L. E.-cell responses noted in this patient. The data suggest that acceleration of improvement was obtained with the leucocyte sediment following the inhibitor extract. This observation supports the suggestion that the inoculated blood produces a therapeutic effect both by the release of DNase inhibitor and the adsorption of the abnormal serum γ-globulin by the structural components of the disrupted leucocytes. Thus, clinical improvement and disappearance of the L. E.-cell phenomenon following hemoinoculation may be due to reduction in the concentration of the circulating abnormal factor as well as to replacement of DNase inhibitor which is destroyed by the mechanism set in motion by the lupus erythematosus factor.

SUMMARY AND CONCLUSIONS

The L. E.-cell phenomenon is thought to represent an in vitro expression of the pathogenesis of systemic lupus. Through a mechanism not presently understood, an abnormal factor develops in the γ-globulin of the serum. This may represent an abnormal immunological phenomenon akin to that found in some cases of hemolytic anemia and thrombocytopenia. The γ-globulin factor is thought to alter mesenchymal cells so that serum proteolytic enzymes gain access to the interior of the cell and destroy the inhibitor of deoxyribonuclease (DNase). Depolymerization of the nuclear deoxyribonucleic acid (DNA) ensues, with cell death and inflammatory reaction. The DNase inhibitor derived from human leucocytes is capable of preventing this phenomenon. On this basis, therapy with fresh compatible blood or leucocyte fractions intramuscularly was attempted in 12 patients with systemic lupus erythematosus. It is felt that the lysis of the infused cells releases their inhibitor of DNase; the structural proteins of the lysed cells may also serve to adsorb the circulating abnormal γ-globulin factor. Therapeutic efficacy is evidenced by reduction in serum DNase activity and clearing of cutaneous eruptions during the first week, followed by disappearance of L. E. cells, fever, pleuritis, pericarditis, myalgias, and arthralgias and improvement in urinary function in three to six weeks. Continuous therapy has maintained patients in remission for a number of months. The occasional exacerbations noted on the withdrawal of steroid therapy are considered to be complications of the induced hypocorticism. The serum DNase activity serves as a useful guide to therapy, since its reduction and rise are the earliest detected measures of the adequacy or inadequacy of the hemotherapuetic dosage.

The results are encouraging and, we believe, deserve extension. However, the great variability in the manifestations of the disease and the occurrence of spontaneous remissions necessitate caution in the interpretation of the data. Proper evaluation of the clinical results awaits the accumulation of a much larger series over a longer period.

REFERENCES

1. Harvey, A. M.; Shulman, L. E.; Tumulty, P. A.; Conley, C. L., and Schoenrich, E. H.: Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases, Medicine **33**:291-437 (Dec.) 1954.

2. Haserick, J. R.: Modern Concepts of Systemic Lupus Erythematosus: A Review of 126 Cases, J. Chronic Dis. **1**:317-334 (March) 1955.

3. Kurnick, N. B.; Schwartz, L.; Pariser, S., and Lee, S.: A Specific Inhibitor for Human Desoxyribonuclease and an Inhibitor of the Lupus Erythematosus Cell Phenomenon from Leucocytes, J. Clin. Invest. **32**:193-201 (March) 1953.

4. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements, the "Tart" Cell and the "L. E." Cell, Proc. Staff Meet. Mayo Clin. **23**:25-28 (Jan.) 1948.

5. Klemperer, P.; Gueft, B.; Lee, S.; Leuchtenberger, C., and Pollister, A. W.: Cytochemical Changes of Acute Lupus Erythematosus, Arch. Path. **49**:503-516 (May) 1950.

6. Carrera, A. E.; Reid, M. V., and Kurnick, N. B.: Differences in Susceptibility of Polymorphonuclear Leucocytes from Several Species to Alteration by Lupus Erythematosus Serum; Application to a More Sensitive L. E. Phenomenon Test, Blood **9**:1165-1171 (Dec.) 1954.

7. Hargraves, M. M.: Systemic Lupus Erythematosus and L. E. Cell Phenomenon, Postgrad. Med. **16**:164-174 (Sept.) 1954.

8. Kurnick, N. B.; Pariser, S.; Schwartz, L.; Lee, S., and Irvine, W.: Studies on Desoxyribonuclease in Systemic Lupus Erythematosus: Nonparticipation of Serum Desoxyribonuclease in the L. E. Phenomenon, J. Clin. Invest. **31**:1036-1041 (Dec.) 1952.

9. Kurnick, N. B.: Desoxyribonuclease Activity of Sera of Man and Some Other Species, Arch. Biochem. **43**:97-107 (March) 1953.

10. Haserick, J. R.; Lewis, L. A., and Bortz, D. W.: Blood Factor in Acute Disseminated Lupus Erythematosus: Determination of Gamma-Globulin as Specific Plasma Fraction, Am. J. M. Sc. **219**: 660-663 (June) 1950.

11. Kurnick, N. B.: Interaction of Serum with the Leucocyte Inhibitor of Desoxyribonuclease and the Lupus Erythematosus Cell Phenomenon, Am. J. Med. **14**:753-754 (June) 1953.

12. Ratnoff, O. D.: The Effect of Clotting on the Spontaneous Activation of Plasmin, J. Clin. Invest. **34**:958 (June) 1955.

13. Slocumb, C. H.: Rheumatic Complaints During Chronic Hypercortisonism and Syndromes During Withdrawal of Cortisone in Rheumatic Patients, Proc. Staff Meet. Mayo Clin. **28**:655-658 (Nov.) 1953.

14. Vander Laan, W. P.: Flexion Deformities in Adrenal Insufficiency, J. Clin. Invest. **34**:968 (June) 1955.

15. Kierland, R. R.; Brunsting, L. A., and O'Leary, P. A.: Quinacrine Hydrochloride (Atabrine) in the Treatment of Lupus Erythematosus, A. M. A. Arch. Dermat. & Syph. **68**:651-660 (Dec.) 1953.

16. Dubois, E. L.: Quinacrine (Atabrine) in Treatment of Systemic and Discoid Lupus Erythematosus, A. M. A. Arch. Int. Med. **94**:131-141 (July) 1954.

17. Pillsbury, D. M., and Jacobson, C.: Treatment of Chronic Discoid Lupus Erythematosus with Chloroquine (Aralen), J. A. M. A. **154**:1330-1333 (April 17) 1954.

18. Reddick, R. H.: Autohemotherapy in Psychiatry, Maryland M. J. **4**:22-31 (Jan.) 1955.

19. Kurnick, N. B., and Radcliffe, I. S.: Effect of Interaction Between DNA and Anti-Malarials on Viscosity and DNase Susceptibility, to be published.

Peptic Ulcer and Pulmonary Emphysema

Their Association in Hospitalized Patients

ELLIOT M. LATTS, M.D.
JAMES F. CUMMINS, M.D.
and
LESLIE ZIEVE, M.D., Minneapolis

For a number of years various clinicians at this institution have been aware of a seemingly high incidence of peptic ulcer in patients with pulmonary emphysema. Little documentation of this association has appeared in the literature, and we have noticed that many physicians are not alert to it. Unrecognized peptic ulceration has been found at postmortem examination in patients with pulmonary emphysema, and in a few instances death has been due to complications of such ulceration. The present review was undertaken to determine the extent of this association in a large representative group of patients.

METHODS AND MATERIALS

Protocols of all patients with the diagnosis of chronic diffuse pulmonary emphysema hospitalized during the years 1950 to 1953 were reviewed. A total of 586 patients was included. Of these, 479 were studied clinically and 107 were autopsied. The clinical diagnoses were recorded at time of discharge by resident physicians and represent the opinions of at least two physicians, one generally being the consulting staff physician. In the majority of instances ordinary clinical criteria such as dyspnea, obstructive breathing on auscultation, anteroposterior enlargement of the chest, decreased cardiac dullness, retraction of rib interspaces on inspiration, and prolonged and slow exhalation at time of vital capacity measurement were used for diagnosis. In many instances specialized respiratory studies were carried out. Chest films were often corroborative.

Such review of records has its weaknesses, which we are well aware of. It is likely that an occasional nonemphysematous patient was included in error. This however is much less likely than the exclusion of milder, and occasionally even severe, cases of emphysema that go undiagnosed. There is thus an unavoidable selective process whereby the sample becomes weighted with patients having moderate or severe emphysema.

The autopsy group included all patients examined post mortem during the aforementioned period who had evidence of diffuse emphysema upon gross examination of the lungs. In 19% the diagnosis was not made clinically, though it was clearly evident at autopsy. As might be expected, a larger proportion of the autopsied group had severe emphysema.

Both the clinical and autopsy emphysema groups were divided into three subgroups: (1) those having a demonstrated peptic ulcer or a demonstrated duodenal deformity at the time of active symptoms, (2) those having symptoms and signs consistent with peptic ulcer but no evident ulcer on a gastrointestinal x-ray series, and (3) those without symptoms or signs or other evidence of an ulcer. There were no significant age differences among the groups or subgroups. The mean age of the nonautopsied patients was 60 ± 8 years (range, 27-82 years), and that of the autopsied group, 61 ± 9 years (range, 26-80 years). Most of the patients were in their sixth decade.

The information available for analysis included the duration and severity of emphysema; the occurrence of cyanosis; vital capacity and carbon-dioxide-combining-power measurements; the duration, type, and complications of peptic ulceration, and, in addition, for the autopsied group, hemoglobin concentration, blood pressure, evidence of chronic cor pul-

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From the Department of Medicine and the Radioisotope Unit, Veterans Administration Hospital and University of Minnesota. Present addresses: Department of Medicine, Veterans Administration Research Hospital, Chicago (Dr. Latts); Department of Medicine, University of Southern California, Los Angeles (Dr. Cummins).

monale, and heart weight. Percentages, means, and standard deviations were calculated where appropriate.

RESULTS AND INTERPRETATIONS

Characteristics of the Patients.—Approximately 50% of the patients in the clinical group on whom an evaluation was recorded had severe pulmonary emphysema, as shown in Table 1. In these patients severity of emphysema was unrelated to the presence or absence of peptic ulceration. Among the autopsied patients a larger proportion of those with peptic ulcers had severe emphysema (χ^2=5.46; P<0.02). A similar difference in percentage incidence of severe emphysema was noted upon comparing the clinical patients with ulcers with the autopsied patients with ulcers (χ^2=7.57; P<0.01).

TABLE 1.—*Percentage of Patients with Severe Pulmonary Emphysema*

Subgroup	Clinical Group		Autopsy Group	
	Cases, No.	% Severe	Cases, No.	% Severe
Peptic ulcer.....	42	50	21	86
No ulcer but S & S *..	40	53	10	50
No ulcer or S & S....	143	53	41	59
All cases.....	225	52	72	65

* Symptoms and signs.

Vital capacity measurements were recorded in approximately three-fourths of the patients. As is well recognized, these measurements generally represent but crudely the degree of pulmonary insufficiency in emphysema. Being the only ventilatory measurement recorded in a large segment of the patients, they are presented for what they are worth. The lowest average value recorded for the clinical group was 2.2 ± 0.9 liters. The lowest average value of the autopsied group was 1.7 ± 0.9 liters, significantly less (t = 3.76; P<0.001). The highest average value recorded for the clinical group was 2.5 ± 0.9 liters, and that for the autopsied group was 2.0 ± 0.9 liters. There were no significant differences among the three subgroups within each of these groups.

Carbon-dioxide-combining-power values were recorded in 65% of the clinical and 85% of the autopsied groups. The highest average value in the clinical group was 29.6 ± 4.3 mEq. per liter. The corresponding value of the autopsied group, 31.9 ± 6.6 mEq. per liter, was significantly higher (t = 3.20; P<0.01). The lowest average values recorded in the clinical and autopsied groups were 27.3 ± 3.6 and 25.5 ± 5.8 mEq. per liter, respectively. Again, there were no significant differences among the subgroups.

Cyanosis was present in 29% of the clinical group and 51% of the autopsied group, a highly significant difference (χ^2=20.2; P<0.001). These are minimum figures, since we assumed cyanosis was absent if not mentioned in the records. The higher incidence among autopsied patients reflects to a large extent the greater severity of their emphysema; however, the comparison is in part spurious, since the existence of cyanosis is more likely to be recorded in the autopsy protocol.

Information concerning the duration of emphysema was available for most of the autopsied group. As a rule, the ulcer patients had a longer history of emphysema. The average duration of emphysema was 17 ± 9 years for 19 patients with ulcer and 13 ± 10 years for 44 patients without ulcer. Sixty-nine per cent of the ulcer patients had their emphysema more than 10 years, in contrast to 59% of those without ulcers (χ^2=4.02; P<0.05).

Incidence of Peptic Ulcer.—The over-all incidence of peptic ulcer in the clinical and autopsy groups is recorded in Table 2, and the incidence of special types of ulcer and their complications is given in Table 3. Peptic ulceration occurred in 15% of the clinical group and 27% of the autopsy group. The difference in incidence is significant (χ^2=8.20; P<0.01) and is probably related to the selective process whereby patients with more prolonged and severe emphysema end up in the autopsied group. Of the clinical group, 37% had either an ulcer or symptoms and signs suggesting an ulcer. Likewise, 43% of the autopsy group had an ulcer or symptoms and signs suggesting an ulcer.

TABLE 2.—*Incidence of Peptic Ulcer*

	No.	%
Clinical group		
Peptic ulcer	74	15.4
No ulcer but S & S*	102	21.3
Ulcer or S & S	176	36.7
No ulcer or S & S	303	63.3
All cases	479	100.0
Autopsy group		
Peptic ulcer	29	27.1
No ulcer but S & S	17	15.9
Ulcer or S & S	46	43.0
No ulcer or S & S	61	57.0
All cases	107	100.0

* Symptoms and signs.

TABLE 3.—*Types of Ulcers and Complications*

	Clinical Group (74 Cases), %	Autopsy Group (29 Cases), %
Gastric ulcer	24	41
Duodenal ulcer	83	79
Both	7	21
Complications		
Bleeding (B)	23	45
Obstruction (O)	15	4
Perforation (P)	8	38
B, O, or P	39	62

A duodenal ulcer was present in approximately 80% of the patients with ulcer. A gastric ulcer was present in 24% of the clinical ulcer group and 41% of the autopsied ulcer group. Approximately one-fifth of the autopsied patients had both gastric and duodenal ulcers. A complication of the ulcer occurred in 39% of those ulcer patients observed clinically and 62% of those examined at autopsy. This difference is probably significant ($\chi^2=4.40$; $P<0.05$).

In the autopsied ulcer group of 29 patients, the ulcer was demonstrated at postmortem examination in 21, a gastric abnormality was present at autopsy though no ulcer was seen at the time of examination in 3, no abnormality was seen in the stomach or duodenum though there had been x-ray demonstration of the ulcer in 4, and the diagnosis was made on clinical grounds only in 1.

Among 15 of the autopsied group with information recorded, the average duration of the ulcer history was 11 ± 9 years, with a range of ½ to 33 years.

REPORT OF CASES

The following case histories illustrate the importance of an awareness of this association.

CASE 1.—A 44-year-old white man was admitted on Oct. 21, 1951, with a history of bronchial asthma since 1940. He had noted progressive increase in frequency and severity of the asthmatic episodes over the years. Twice previously he was admitted for pulmonary emphysema with superimposed bronchitis and pneumonitis. Three weeks prior to admission he had observed increasing exertional dyspnea, orthopnea, and cough productive of 1 cupful of sputum daily. Ten days before admission he first noted ankle edema. A duodenal ulcer was first observed in 1943, and an episode of gastrointestinal bleeding was treated in 1950. A diagnosis of diabetes mellitus was made on the last admission. He had been treated on previous occasions with cortisone and corticotropin in addition to various bronchodilator drugs.

Examination revealed an obese man who was moderately cyanotic and in acute severe respiratory distress. Blood pressure was 180/80 mm. Hg. His chest was hyperresonant to percussion, and diaphragmatic excursions were decreased bilaterally. Expiration was prolonged. There were wheezes, rhonchi, and moist rales throughout both lung fields. Pitting edema of the ankles was present bilaterally. His arm-to-tongue circulation time was 14 seconds, and venous pressure was 14 cm. of water.

Urinalysis was normal except for 3+ sugar. WBC count on admission was 18,150/cu. mm. and remained in this range until the day of death, when it rose to 63,200/cu. mm. Hemoglobin (Hb.) varied from 12 to 16 gm/100 cc. Sedimentation rate was 1 mm. in an hour. On admission the carbon-dioxide-combining power (CO_2) was 37 mEq/liter, and it gradually fell to 23 mEq/liter on the day of death. Blood pH the day after admission was 7.20, and two days later it was 7.32. Fasting blood sugar was 105 mg/100 cc. Sputum cultures showed Neisseria catarrhalis and streptococci. Marked right axis deviation was evident on the ECG. Chest x-ray showed the changes of emphysema with blebs in the right lower lobe. The heart was moderately enlarged.

He was placed on a sodium-restricted diabetic diet. In spite of repeated injections of aminophylline, epinephrine, and penicillin, plus oxygen by mask, he continued in acute distress. He became progressively more lethargic and less responsive; consequently, the oxygen was discontinued, with improvement in his mental status and, to a slight degree, in his respiratory distress. Thereafter he seemed to improve slightly until the seventh hospital day, when he complained of abdominal pain and experienced

an exacerbation of his respiratory distress. Examination at this time revealed abdominal distention and normal bowel sounds. The following morning there was in addition abdominal rigidity, which was thought to be due to the acute respiratory distress. Emergency laboratory and x-ray studies were ordered, but before these could be completed the patient was found dead, sitting on the commode. The interval between admission and death was eight days.

Autopsy Report.—The left lung weighed 550 gm.; the right, 650 gm. There were numerous emphysematous blebs over the entire surfaces of both lungs, measuring up to 6 cm. in diameter. There was minimal secretion in the bronchial tree. The heart weighed 580 gm. The left ventricular wall was 2 cm. in thickness, and the right, 9 mm. The coronary arteries showed mild atherosclerosis. The stomach revealed several small ulcerations with hyperemic borders. In the duodenum was an ulcer crater measuring 1.5×1.5 cm., at the base of which was a 7 mm. linear perforation. The remainder of the gastrointestinal tract was normal. There was no blood in the bowel. Microscopic sections of the lungs revealed severe emphysema with increased fibrosis. There was no evidence of pneumonia. The ulcer was surrounded by considerable polymorphonuclear and round-cell infiltration. The peritoneal reaction was minimal.

CASE 2.—A 62-year-old man was admitted on Nov. 24, 1952, with many complaints, the foremost of which were difficulty in breathing, epigastric pain of two weeks' duration, and marked weakness. He had mildly progressive exertional dyspnea for 10 years but no edema, orthopnea, or nocturnal dyspnea. His dyspnea was associated for many years with a chronic cough productive of yellowish mucoid sputum. One month prior to admission his dyspnea and cough became worse and were associated with wheezing and 1 to 2 cupfuls of greenish sputum daily. An episode of this type had been a yearly event and usually lasted two to four weeks.

He had an old duodenal ulcer which led to a gastroenterostomy in 1919. Subsequently the ulcer flared up intermittently and was easily handled by two or three days of a milk diet. His appetite had been poor generally, but his weight remained constant until the present episode of dyspnea occurred, when he lost 10 to 15 lb. Bowel movements were regular, and melena was never noted.

He had had Buerger's disease since the first world war. His last chest x-ray revealed a density in the right lung field which was variously interpreted as atelectasis or pneumonitis of the right middle lobe.

At the time of admission he was in moderate respiratory distress with mild cyanosis. The temperature was 99.6 F; pulse, 80 beats per minute; blood pressure, 130/70 mm. Hg. He had the typical chest findings of emphysema with increased anteroposterior diameter and fixed diaphragms. Breath sounds were decreased, and there were numerous bilateral rhonchi, wheezes, and coarse musical rales. Vital capacity was 1.5 liters expelled slowly. His heart was normal. Slight tenderness was elicited in the epigastrium.

Urinalysis was negative; hemoglobin on admission was 11.7 gm/100 cc.; white cell count was 15,600/cu. mm., with 85% neutrophiles and 7% lymphocytes. Sedimentation rate was 62 mm. in an hour. CO_2 was 27.5 mEq/liter; chlorides, 99 mEq/liter, and BUN, 20 mg/100 cc. ECG revealed a right bundle branch block. A chest x-ray showed a triangular shadow in the right midlung field which was thought to be a right middle lobe pneumonitis.

Throughout hospitalization he complained of back pain, weakness, and dyspnea and had a low-grade fever. He received penicillin without effect. A stool examination for occult blood was positive on admission, although subsequent examinations were negative. Five days after admission he complained of transient dizziness and greater weakness and became mildly hypotensive. No other findings were noted. The next day he was found in shock, having vomited blood and passed two stools that were grossly bloody. Hemoglobin concentration at this time was 9 gm/100 cc. In spite of blood transfusions amounting to 4500 ml. given over the next seven hours, he deteriorated rapidly and died. The interval between admission and death was seven days.

Autopsy Report.—The right lung weighed 820 gm.; the left, 875 gm. Extensive emphysema was evident grossly. Bullae up to 2 cm. in diameter were seen on the surface of the left lung. All the major bronchi of both lungs contained bloody mucus. The heart weighed 425 gm.; the left ventricle, 100 gm.; the right, 75 gm. The coronary arteries were patent throughout. The liver weighed 1950 gm. and appeared normal. A gastrojejunostomy was present. The stomach and small and large intestines were greatly distended with blood, which was red high in the small bowel and tarry in the large bowel. A 5×4 cm. ulcer crater was located on the lesser curvature of the stomach.

Microscopically the lungs were severely emphysematous. This was associated with a diffuse bronchitis. In one section pulmonary edema was described. The large ulcer crater was benign and extended to the serosa. Leading up to the necrotic floor of the ulcer was a large artery containing a recent small thrombus. The myocardium was normal.

CASE 3.—A 58-year-old white man was first seen in 1927 complaining of a severe chronic productive cough, weakness, and dyspnea which fol-

lowed an episode of pneumonia in 1918. In 1928 he was found to have a duodenal ulcer, and in 1930 a diagnosis of pulmonary emphysema was made. During the next 22 years he had numerous hospital admissions because of pulmonary emphysema with superimposed chronic bronchitis and (or) pneumonitis. In 1952 he developed pedal edema and his liver became palpable. His carbon-dioxide-combining power at that time was 39 mEq/liter, and his vital capacity was 0.5 liters expelled slowly. A diagnosis of cor pulmonale was made, and the patient was placed on digitoxin and sodium restriction.

He was admitted for the last time on May 18, 1953, because of progressive ankle edema, dyspnea, and oliguria. At that time he was poorly nourished, cyanotic, and severely dyspneic. His blood pressure was 110/80 mm. Hg; pulse rate, 100; temperature, 98.6 F. His chest was markedly emphysematous, with increased resonance on percussion and decreased breath sounds throughout. The vital capacity was again 0.5 liters slowly expired. His heart appeared enlarged to the left. His liver was palpable 6 cm. below the costal margin and was nontender. Moderate pitting edema of the lower extremities was present.

The significant laboratory data included a Hb. of 15.7 gm/100 cc., normal WBC and differential counts, sedimentation rate of 11 mm. in an hour, and CO_2 of 38 mEq/liter. An ECG showed a right strain pattern.

He was given a 200 mg. sodium diet, digitoxin, aminophylline, and penicillin, and was getting along rather poorly when he developed upper abdominal pain approximately 10 days after admission. A chest x-ray taken five days later revealed free air under the diaphragms, and the diagnosis of perforated duodenal ulcer was suspected for the first time. He was started on continuous gastric suction, intravenous fluids, and additional antibiotic therapy. He improved somewhat temporarily, but one week later he became despondent over his condition and made an unsuccessful suicidal attempt. The following day he lapsed into coma after the onset of auricular fibrillation and died. One day before death his BUN was 17 mg/100 cc.; CO_2, 46 mEq/liter; potassium, 4.9 mEq/liter; sodium, 135 mEq/liter, and chlorides, 76 mEq/liter. The interval between admission and death was 23 days.

Autopsy Report.—The heart weighed 475 gm. The right atrium was markedly dilated and contained a large thrombus. The right ventricle weighed 107 gm. and was 12 mm. in thickness; the left weighed 94 gm. and was 15 mm. in thickness. The left lung weighed 325 gm., and the right, 500 gm. Numerous emphysematous blebs were present over the surfaces of both lungs. The bronchi on the left contained a small amount of mucoid material, and the right bronchi were filled with thick yellowish material. The abdominal cavity contained about 1500 ml. of slightly cloudy amber fluid. The surfaces of the bowel and peritoneum were smooth and shiny. On the anterior wall of the duodenum was an ulcer measuring 1.0×0.4 cm., which had perforated. There was some yellowish fibrinous material around the site of perforation. There was also a 4 mm. superficial ulcer on the posterior wall of the duodenum. The large intestine contained a small amount of tarry stool. No fresh blood was noted. Microscopic sections of the lungs showed many ruptured septa and marked bleb formation. Sections through the duodenum showed no scarring nor marked inflammation around the perforation. There was chronic passive congestion of the liver and kidneys.

CASE 4.—A 62-year-old white man was admitted on Nov. 7, 1951, with a three-day history of melena. A duodenal ulcer was previously diagnosed in May, 1951, following an episode of gastrointestinal bleeding. A second similar episode of bleeding followed in October, 1951. The patient had had several hospital admissions since 1947 because of pulmonary emphysema, pulmonary fibrosis, chronic bronchitis, pneumonia, and peripheral neuritis. He had been a chronic alcoholic for about 15 years.

On physical examination he was very orthopneic and cyanotic and appeared chronically ill. His blood pressure was 130/80 mm. Hg. An emphysematous configuration of his chest with an increase in the anteroposterior diameter was apparent. His diaphragms were low and moved poorly, and his chest was hyperresonant on percussion. Expiratory wheezes were heard posteriorly, and coarse rales, anteriorly. Vital capacity was 1.2 liters, expelled slowly. His liver was palpated 6 cm. below the right costal margin and was nontender. By percussion its upper border was at the costal margin. Rectal examination revealed a tarry stool. There was clubbing of his fingers, and the nailbeds were cyanotic.

Significant laboratory data included a Hb. of 14.2 gm/100 cc; WBC count of 25,000/cu. mm., with 94% polymorphonuclear cells; sedimentation rate of 40 mm. in an hour. BUN was 20 mg/100 cc.; CO_2, 33 mEq/liter, and Cl, 85 mEq/liter. Pulmonary fibrosis and severe pulmonary emphysema were seen in the x-ray of the chest. Sinus tachycardia and right ventricular strain pattern were apparent on the electrocardiogram.

The patient was placed on an ulcer regimen, aminophylline, and penicillin. He continued very cyanotic and dyspneic and complained of mild to moderately severe burning epigastric pain. Stools on two occasions were guaiac-positive. He had a low-grade fever (temperature up to 99.8 F). On the third hospital day it was noted that he was confused and restless. The following morning while

at his bedside the patient fell to the floor and had a grand mal convulsive seizure. He had evident peripheral circulatory collapse. Abdominal examination at this time revealed moderate epigastric tenderness and resistance. Bowel sounds were minimal. His hemoglobin was 14.6 gm/100 cc. An abdominal catastrophe was considered but not seriously. He was given oxygen and digitoxin but failed to respond and died four hours later. The interval between admission and death was four days.

Autopsy Report.—The left lung weighed 400 gm., and the right, 550 gm. Both were voluminous and did not collapse. Occasional emphysematous blebs were noted on the surfaces. The bronchi were filled with sticky mucoid exudate. The heart weighed 300 gm. The left ventricle measured 2 cm., and the right ventricle, 4 mm. in thickness. There was extreme coronary sclerosis of the left anterior descending and right coronary arteries but no complete occlusion. The liver weighed 1350 gm. and on cut section had a yellowish tinge. The esophagus and stomach showed no abnormalities. Immediately beyond the pylorus there was a 2 cm. perforation in the duodenal wall posteriorly. The remainder of the duodenal cap was very scarred. There was approximately 350 ml. of greenish cloudy fluid in the lesser omental sac. The involved area extended into the free abdominal cavity as well as the left subdiaphragmatic area. The remainder of the intestinal tract revealed no abnormalities except for the exudate on its surface secondary to peritonitis.

Microscopically the lungs were markedly emphysematous. Many of the small and large bronchi were filled with mucopurulent exudate. The submucosal area in these bronchi was infiltrated with pus cells, and there were many small areas of interstitial pneumonitis surrounding the smaller bronchi. Sections of the stomach revealed an antral gastritis. On the serosal surface of the stomach there was a heavy inflammatory exudate with necrotic debris. The base of the duodenal ulcer showed chronic inflammatory reaction, and sections through it revealed an ulcerated and thrombosed artery. The liver showed moderate fatty metamorphosis but no evidence of portal cirrhosis.

CASE 5.—A 57-year-old retired farmer was admitted on Oct. 20, 1952, with a 12-year history of emphysema. Two weeks before admission he developed an upper respiratory infection with exacerbation of his symptoms. Examination revealed him to be thin, apprehensive, and dyspneic. His temperature was 100 F; blood pressure, 150/100 mm. Hg. His chest was markedly emphysematous, and expiration was prolonged. Breath sounds were barely audible. His stool was tarry on rectal examination. His hemoglobin was 10.8 gm/100 cc.; WBC count 13,000/cu. mm., with 82% polymorphonuclear cells; BUN, 17 mg/100 cc.; CO_2, 34.7 mEq/liter. Two weeks later his CO_2 was 40.1 mEq/liter. His ECG showed auricular tachycardia, peaked P waves, marked clockwise rotation, and nonspecific T wave changes. On chest x-ray he had bilateral upper lobe fibrosis and numerous blebs on the left. His stools were guaiac-positive.

Shortly after admission he lapsed into shock after having a small coffee-ground emesis. With transfusions his hemoglobin rose to 12 gm/100 cc. and blood pressure rose to 150/100 mm. Hg, stabilizing at these levels. A few days after admission he developed a small right pneumothorax. He received oxygen intermittently in addition to bronchial dilators and antibiotics but continued restless and dyspneic. Four days before death he had an episode of extreme dyspnea, cyanosis, and restlessness and became comatose for several hours. His blood pressure varied between 110-170/60-110 mm. Hg, and his pulse remained rapid. Following this episode he continued to do poorly, and three days later he again became comatose and died. The interval between admission and death was 14 days.

Autopsy Report.—The heart weighed 410 gm. and appeared grossly normal except for moderate coronary arteriosclerosis. The right lung was partially collapsed. Each lung weighed 450 gm. and had numerous blebs. On cut section the lungs were dark red and moist. The stomach contained about 100 ml. of greenish-yellow semifluid material. An ulcer was found on the superior wall of the first portion of the duodenum which measured 6×6 cm. and had sharply defined undermined edges. The base of the ulcer was covered by an adherent clot. Distal to the ulcer the entire small bowel was filled with dark red and tarry material.

Microscopic examination of the lungs showed the characteristic appearance of extensive emphysema. The bronchi contained suppurative material and were surrounded by small peribronchial areas of acute inflammation. A section through the ulcer crater showed deep penetration into the muscle by an acute process with polymorphonuclear infiltration.

CASE 6.—A 68-year-old meat cutter was admitted Aug. 16, 1952, complaining of progressive dsypnea and orthopnea of two months' duration. He had a 15-year history of chronic productive cough with recurrent episodes of bronchitis for several years prior to this admission. He had been anorexic and lost 20 lb. during the present illness. He had been treated with a variety of bronchodilators but obtained little relief except with epinephrine. Examination revealed an emaciated cyanotic elderly man in moderate respiratory distress. Temperature was 97.8 F; pulse rate, 98, blood pressure, 130/70 mm. Hg. His neck veins were slightly distended, and his lips and ears were slightly cyanotic. He had a barrel-shaped hyperresonant chest, and there were

numerous moist musical rales throughout both lung fields. His vital capacity was less than 1 liter, and he exhaled slowly. His abdomen was tense, making examination difficult, but no tenderness was elicited.

His hemoglobin was 13.1 gm/100 cc., and white blood cell count, 6500/cu. mm., with 89% neutrophiles. Urinalysis was negative except for albuminuria. His BUN was 11 mg/100 cc.; CO_2, 35 mEq/liter; Cl, 95 mEq/liter. Chest x-ray showed moderately severe bilateral pulmonary emphysema and fibrosis. An ECG revealed a nodal tachycardia and right bundle branch block. Six days before death the block disappeared.

He was treated with penicillin, aqueous epinephrine, ephedrine, and aminophylline. His dyspnea and orthopnea decreased, but he was never free of respiratory distress. He developed bladder atony, which was relieved when the ephedrine was discontinued. He became more cyanotic and lethargic, following a progressive course until death, which was presumably due to respiratory insufficiency. The interval between admission and death was 30 days.

Autopsy Report.—One liter of clear fluid was found in the abdominal cavity and 750 ml. in each side of the thorax. The heart weighed 450 gm., the ratio of left to right ventricle being 1.70. The lungs did not collapse after the chest was opened; each weighed 550 gm. Numerous emphysematous blebs were present bilaterally. There was considerable thick mucus in the major bronchi bilaterally and atelectasis of the basilar portions of the right and left lower lobes. The liver weighed 1375 gm. and showed passive congestion. The stomach was normal. Just distal to the pylorus was a deep ulcer which appeared to have penetrated into pancreatic tissue. Two other small superficial ulcers were found in the jejunum. The small intestine contained considerable blood and tarry material, estimated volume 750 ml.

Microscopic examination of the lungs revealed many large blebs with rupture of interalveolar septa. Some areas showed marked thickening of the septa and fibrosis; others showed atelectasis. The perforating duodenal ulcer had penetrated through the entire wall into necrotic fat beneath. This area was surrounded by a thin margin of mononuclear cells. Superficial layers of adjacent duodenal mucosa showed some lymphocytic infiltration.

MISCELLANEOUS CHARACTERISTICS OF EMPHYSEMA PATIENTS

Certain miscellaneous information was available in the autopsied group of 107 patients. The average hemoglobin concentration was 12.7 ± 2.9 gm/100 cc., with a range of 4.5 to 19.0 gm/100 cc. Values of 17 gm/100 cc. or more were observed in 5% of the patients; values of 16 gm/100 cc. or more, in 12%. Values less than 10 gm/100 cc. were observed in 16% of patients, and values less than 12 gm/100 cc., in 35%. There were no significant differences among the subgroups in hemoglobin concentration. Clubbing of fingers was mentioned infrequently and undoubtedly occurred more often than was recorded; however, where mentioned it was always associated with polycythemia and cyanosis. Chronic cor pulmonale was present in only 14%, though chronic passive congestion of the liver was noted in 65%.

The average blood pressure of these patients was 132/81 ± 30/17 mm. Hg, with a range of 88-220/50-135 mm. Hg. Again, no differences were evident among the subgroups.

Heart weights were recorded in 104 patients. The average weight was 420 ± 117 gm. (range, 240-775 gm.). Separate ventricle weights were also available in 73 patients. The average right ventricle weighed 84 ± 37 gm. (range, 25-176 gm.); left ventricle, 132 ± 55 gm. (range, 65-325 gm.). The average ratio of left to right ventricle was 1.74 ± 0.71 (range, 0.59-4.10). This compares with the normal average of 1.67 at our hospital. No significant differences were noted among the subgroups.

It was of interest to record other associated diseases observed at autopsy. Hypertensive or arteriosclerotic heart disease was noted in 48%. Bronchitis was present in 22%; pneumonitis, in 33%; pulmonary infarction, in 20%, and atelectasis, in 11%. Tuberculosis and bronchogenic carcinoma were each noted in fewer than 10% of patients. A given patient generally had more than one of these associated diseases. The average number of diagnoses of major diseases recorded per patient was 3.9. This was significantly greater than the figure of 2.5 observed in the clinical group (t=9.86; $P<10^{-8}$). The corresponding averages for the ulcer patients only were 4.3 for the autopsy group and

3.5 for the clinical group. The number of major diagnoses per patient varied from one to seven for both groups.

COMMENT

From this analysis of hospitalized patients with pulmonary emphysema we would conclude that approximately one-fifth of such patients have associated a demonstrable peptic ulcer and two-fifths have either an ulcer or symptoms and signs thereof. Patients with both emphysema and demonstrated peptic ulcer comprised 0.69% of 39,486 patients hospitalized at this institution during the five-year period from 1950 to 1954. Pulmonary emphysema patients comprised 3.45% of all hospitalized patients; those with peptic ulcer, 5.53%. By chance alone the occurrence of the two together would have been 0.19%. The observed incidence in hospitalized patients was thus 3.6 times the chance value. These incidence figures refer only to hospitalized patients and are not applicable to emphysema patients in general.

The only comparable previous report, that of Green and Dundee,[1] gave similar results. They observed peptic ulceration in 19% of 64 autopsied patients with emphysema and a like percentage of 72 clinically observed patients. Fulton [2] found evidence of peptic ulceration at autopsy incidentally in 18% of 42 patients with chronic pulmonary emphysema.

The converse approach to this problem concerns the incidence of pulmonary emphysema in patients with peptic ulceration. This has been studied by Hirvonen and Perttila,[3] who found pulmonary emphysema in approximately 35% of men with stomach ulcers (34% of 1005 clinical and 39% of 285 autopsy cases in age range of 21-80 years) in contrast to approximately 20% of men without ulcers (assuming a similar age distribution, which was not given in the report). Weber and Gregg [4] similarly observed chronic pulmonary disease, largely emphysema and fibrosis, in 43% of 70 patients with gastric ulcer in contrast to a control incidence of 10%.

The association between pulmonary emphysema and peptic ulceration is sufficiently prominent to make us routinely suspect peptic ulceration in any emphysematous patient with gastrointestinal symptoms. Physician awareness of this relationship should aid greatly in avoiding some of the serious complications we have seen.

How do we account for the association? There are few factual data on which to base an explanation, however one may speculate as to the importance of several factors. Apparently, acidosis per se has little influence upon gastric acid secretion, whereas carbon dioxide (CO_2) content of blood has a significant effect.[5] Apperly and Crabtree [6] noted a moderately high correlation between CO_2 capacity of arterial blood plasma and the total gastric acidity in 18 healthy students. Browne and Vineberg [7] noted a direct relationship between CO_2 content of blood and gastric acid secretion following vagal stimulation but not following histamine stimulation in dogs. It is possible that a similar relationship exists between CO_2 tension and gastric acid secretion in the patient with emphysema.

Emotional factors may also play a contributory role in view of the observation of Wolf and Wolff [8] that periods of hostility and resentment—common emotional moods in emphysematous patients—result in increased acid secretion.

Hormonal factors are possibly of major significance in the production of peptic ulcera tion. As a chronic stress state, pulmonary emphysema may result in increased secretion of corticoids which in turn stimulate excessive acid secretion.[9] Clearly, the use of steroids therapeutically in emphysematous patients should be approached with caution.

It is most likely that a combination of conflicting factors are operative in emphysema. For example, anoxia, when severe, depresses gastric secretion,[10] whereas the associated increased CO_2 tension probably results in increased gastric acidity. The net effect of the several factors involved is apparently to increase peptic activity in emphysema.

The exact role and relative significance of each factor can be studied most profitably in the emphysema patient himself by direct simultaneous measurement of variables such as CO_2 tension, gastric acid secretion, uropepsin excretion, and corticoid excretion, among others. This remains to be done, and until it is done explanations of this association will remain simply conjectures.

SUMMARY

The association of peptic ulcer with chronic diffuse pulmonary emphysema has been studied in 586 hospitalized male patients, 479 observed clinically and 107 examined after death. Most of the patients were in their sixth decade, the average age being approximately 60 years. The emphysema was severe in 50%-65% of the patients.

Peptic ulceration, duodenal or gastric, was demonstrated in approximately one-fifth of the emphysema patients, and an ulcer or symptoms and signs suggesting an ulcer was present in approximately two-fifths. Approximately 80% of the peptic ulcers were duodenal. A serious complication of the ulcer occurred in two-fifths of those ulcer patients observed clinically and three-fifths of those seen at autopsy.

The association of peptic ulcer with pulmonary emphysema is sufficiently prominent to make us routinely suspect peptic ulceration in any emphysematous patient with vague gastrointestinal distress.

REFERENCES

1. Green, P. T., and Dundee, J. C.: The Association of Chronic Pulmonary Emphysema with Chronic Peptic Ulceration, Canad. M. A. J. **67**: 438, 1952.

2. Fulton, R. M.: The Heart in Chronic Pulmonary Emphysema, Quart. J. Med. **22**:43, 1953.

3. Hirvonen, M., and Perttila, M.: Lungemfysem vid vissa sjukdomar, speciellt magsar, Nord. med. **45**:513, 1951.

4. Weber, J. M., and Gregg, L. A.: The Coincidence of Benign Gastric Ulcer and Chronic Pulmonary Disease, Ann. Int. Med. **42**:1026, 1955.

5. Babkin, B. P.: Secretory Mechanism of the Digestive Glands, New York, Paul B. Hoeber, Inc., 1950.

6. Apperly, F. L., and Crabtree, M. G.: The Relation of Gastric Function to the Chemical Composition of the Blood, J. Physiol. **73**:331, 1931.

7. Browne, J. S. L., and Vineberg, A. M.: The Interdependence of Gastric Secretion and the CO_2 Content of the Blood, J. Physiol. **75**:345, 1932.

8. Wolf, S., and Wolff, H. G.: Human Gastric Function, New York, Oxford University Press, 1947, p. 139.

9. Zubiran, J. M.; Kark, A. E., and Dragstedt, L. R.: The Effect of ACTH on Gastric Secretion in Experimental Animals, Gastroenterology **21**: 276, 1952.

10. Von Liere, E. J.: Anoxia: Its Effect on the Body, Chicago, University of Chicago Press, 1942.

A Contribution to the Philosophy of Medicine

The Basic Models of the Doctor-Patient Relationship

THOMAS S. SZASZ, M.D., Bethesda, Md.
and
MARC H. HOLLENDER, M.D., Chicago

INTRODUCTION

When a person leaves the culture in which he was born and raised and migrates to another, he usually experiences his new social setting as something strange—and in some ways threatening—and he is stimulated to master it by conscious efforts at understanding. To some extent every immigrant to the United States reacts in this manner to the American scene. Similarly, the American tourist in Europe or South America "scrutinizes" the social setting which is taken for granted by the natives. To scrutinize—and criticize—the pattern of other peoples' lives is obviously both common and easy. It also happens, however, that people exposed to cross cultural experiences turn their attention to the very customs which formed the social matrix of their lives in the past. Lastly, to study the "customs" which shape and govern one's day-to-day life is most difficult of all.[1]

In many ways the psychoanalyst is like a person who has migrated from one culture to another. To him the relationship between physician and patient—which is like a custom that is taken for granted in medical practice and which he himself so treated in his early history—has become an object of study. While the precise nature and extent of the influence which psychoanalysis and so-called dynamic psychiatry have had on modern medicine are debatable, it seems to us that the most decisive effect has been that of making physicians explicitly aware of the possible significance of their relationship to patients.

The question naturally arises as to "What is a doctor-patient relationship?" It is our aim to discuss this question and to show that certain philosophical preconceptions associated with the notions of "disease," "treatment," and "cure" have a profound bearing on both the theory and the practice of medicine.*

WHAT IS A HUMAN RELATIONSHIP?

The concept of a relationship is a novel one in medicine. Traditionally, physicians have been concerned with "things," for example, anatomical structures, lesions, bacteria, and the like. In modern times the scope has been broadened to include the concept of "function." The phenomenon of a human relationship is often viewed as though it were a "thing"or a "function." It is, in fact, neither. Rather it is an abstraction, appropriate for the description and handling of certain observational facts. Moreover, it is

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Commander (MC), U. S. N. R.; Department of Psychiatry, U. S. Naval Hospital, National Naval Medical Center; Staff Member, Institute for Psychoanalysis, Chicago, on leave of absence (Dr. Szasz), and Staff Member, Institute for Psychoanalysis, and Associate Professor of Psychiatry, University of Illinois College of Medicine (Dr. Hollender).

* In our approach to this subject we have been influenced by psychologic (psychoanalytic), sociologic, and philosophic considerations. See in this connection References 2-4 and Szasz, T. S.: On the Theory of Psychoanalytic Treatment, read before the Annual Meeting of the American Psychoanalytic Association, Atlantic City, N. J., May 7, 1955; Internat. J. Psychoanal., to be published.

an abstraction which presupposes concepts of both structure and function.

The foregoing comments may be clarified by concrete illustrations. Psychiatrists often suggest to their medical colleagues that the physician's relationship with his patient "per se" helps the latter. This creates the impression (whether so intended or not) that the relationship is a thing, which works not unlike the way that vitamins do in a case of vitamin deficiency. Another idea is that the doctor-patient relationship depends mainly on what the physician does (or thinks or feels). Then it is viewed not unlike a function.

When we consider a relationship in which there is joint participation of the two persons involved, "relationship" refers to neither a structure nor a function (such as the "personality" of the physician or patient). It is, rather, an abstraction embodying the activities of two interacting systems (persons).[5]

TABLE 1.—*Three Basic Models of the Physician-Patient Relationship*

	Model	Physician's Role	Patient's Role	Clinical Application of Model	Prototype of Model
1.	Activity-passivity	Does something to patient	Recipient (unable to respond or inert)	Anesthesia, acute trauma, coma, delirium, etc.	Parent-infant
2.	Guidance-cooperation	Tells patient what to do	Cooperator (obeys)	Acute infectious processes, etc.	Parent-child (adolescent)
3.	Mutual participation	Helps patient to help himself	Participant in "partnership" (uses expert help)	Most chronic illnesses, psychoanalysis, etc.	Adult-adult

THREE BASIC MODELS OF THE DOCTOR-PATIENT RELATIONSHIP

The three basic models of the doctor-patient relationship (see Table 1), which we will describe, embrace modes of interaction ubiquitous in human relationships and in no way specific for the contact between physician and patient. The specificity of the medical situation probably derives from a combination of these modes of interaction with certain technical procedures and social settings.

1. *The Model of Activity-Passivity.*—Historically, this is the oldest conceptual model. Psychologically, it is not an interaction, because it is based on the effect of one person on another in such a way and under such circumstances that the person acted upon is unable to contribute actively, or is considered to be inanimate. This frame of reference (in which the physician does something to the patient) underlies the application of some of the outstanding advances of modern medicine (e. g., anesthesia and surgery, antibiotics, etc.). The physician is active; the patient, passive. This orientation has originated in—and is entirely appropriate for—the treatment of emergencies (e. g., for the patient who is severely injured, bleeding, delirious, or in coma). "Treatment" takes place irrespective of the patient's contribution and regardless of the outcome. There is a similarity here between the patient and a helpless infant, on the one hand, and between the physician and a parent, on the other. It may be recalled that psychoanalysis, too, evolved from a procedure (hypnosis) which was based on this model. Various physical measures to which psychotics are subjected today are another example of the activity-passivity frame of reference.

2. *The Model of Guidance-Cooperation.*—This model underlies much of medical practice. It is employed in situations which are less desperate than those previously mentioned (e. g., acute infections). Although the patient is ill, he is conscious and has feelings and aspirations of his own. Since he suffers from pain, anxiety, and other distressing symptoms, he seeks help and is ready and willing to "cooperate." When he turns to a physician, he places the latter (even if only in some limited ways) in a

position of power. This is due not only to a "transference reaction" (i. e., his regarding the physician as he did his father when he was a child) but also to the fact that the physician possesses knowledge of his bodily processes which he does not have. In some ways it may seem that this, like the first model, is an active-passive phenomenon. Actually, this is more apparent than real. Both persons are "active" in that they contribute to the relationship and what ensues from it. The main difference between the two participants pertains to power, and to its actual or potential use. The more powerful of the two (parent, physician, employer, etc.) will speak of guidance or leadership and will expect cooperation of the other member of the pair (child, patient, employee, etc.). The patient is expected to "look up to" and to "obey" his doctor. Moreover, he is neither to question nor to argue or disagree with the orders he receives. This model has its prototype in the relationship of the parent and his (adolescent) child. Often, threats and other undisguised weapons of force are employed, even though presumably these are for the patient's "own good." It should be added that the possibility of the exploitation of the situation—as in any relationship between persons of unequal power—for the sole benefit of the physician, albeit under the guise of altruism, is ever present.

3. *The Model of Mutual Participation.*—Philosophically, this model is predicated on the postulate that equality among human beings is desirable. It is fundamental to the social structure of democracy and has played a crucial role in occidental civilization for more than two hundred years. Psychologically, mutuality rests on complex processes of identification—which facilitate conceiving of others in terms of oneself—together with maintaining and tolerating the discrete individuality of the observer and the observed. It is crucial to this type of interaction that the participants (1) have approximately equal power, (2) be mutually interdependent (i. e., need each other), and (3) engage in activity that will be in some ways satisfying to both.

This model is favored by patients who, for various reasons, want to take care of themselves (at least in part). This may be an overcompensatory attempt at mastering anxieties associated with helplessness and passivity. It may also be "realistic" and necessary, as, for example, in the management of most chronic illnesses (e. g., diabetes mellitus, chronic heart disease, etc.). Here the patient's own experiences provide reliable and important clues for therapy. Moreover, the treatment program itself is principally carried out by the patient. Essentially, the physician helps the patient to help himself.

In an evolutionary sense, the pattern of mutual participation is more highly developed than the other two models of the doctor-patient relationship. It requires a more complex psychological and social organization on the part of both participants. Accordingly, it is rarely appropriate for children or for those persons who are mentally deficient, very poorly educated, or profoundly immature. On the other hand, the greater the intellectual, educational, and general experiential similarity between physician and patient the more appropriate and necessary this model of therapy becomes.

THE BASIC MODELS AND THE PSYCHOLOGY OF THE PHYSICIAN

Consideration of why physicians seek one or another type of relationship with patients (or seek patients who fit into a particular relationship) would carry us beyond the scope of this essay. Yet, it must be emphasized that as long as this subject is approached with the sentimental viewpoint that a physician is simply motivated by a wish to help others (not that we deny this wish), no scientific study of the subject can be undertaken. Scientific investigation is possible only if value judgment is subrogated, at least temporarily, to a candid scrutiny of the physician's actual behavior with his patients.

The activity-passivity model places the physician in absolute control of the situation. In this way it gratifies needs for mastery and contributes to feelings of superiority.† At the

† References 6 and 7.

same time it requires that the physician disidentify with the patient as a person.

Somewhat similar is the guidance-cooperation model. The disidentification with the patient, however, is less complete. The physician, like the parent of a growing child, could be said to see in the patient a human being potentially (but not yet) like himself (or like he wishes to be). In addition to the gratifications already mentioned, this relationship provides an opportunity to recreate and to gratify the "Pygmalion Complex." Thus, the physician can mold others into his own image, as God is said to have created man (or he may mold them into his own image of what they should be like, as in Shaw's "Pygmalion"). This type of relationship is of importance in education, as the transmission of more or less stable cultural values (and of language itself) shows. It requires that the physician be convinced he is "right" in his notion of what is "best" for the patient. He will then try to induce the patient to accept his aims as the patient's own.

The model of mutual participation, as suggested earlier, is essentially foreign to medicine. This relationship, characterized by a high degree of empathy, has elements often associated with the notions of friendship and partnership and the imparting of expert advice. The physician may be said to help the patient to help himself. The physician's gratification cannot stem from power or from the control over someone else. His satisfactions are derived from more abstract kinds of mastery, which are as yet poorly understood.

It is evident that in each of the categories mentioned the satisfactions of physician and patient complement each other. This makes for stability in a paired system. Such stability, however, must be temporary, since the physician strives to alter the patient's state. The comatose patient, for example, either will recover to a more healthy, conscious condition or he will die. If he improves, the doctor-patient relationship must change. It is at this point that the physician's inner (usually unacknowledged) needs are most likely to interfere with what is "best" for the patient. At this juncture, the physician either changes his "attitude" (not a consciously or deliberately assumed role) to complement the patient's emergent needs or he foists upon the patient the same role of helpless passivity from which he (allegedly) tried to rescue him in the first place. Here we touch on a subject rich in psychological and sociological complexities. The process of change the physician must undergo to have a mutually constructive experience with the patient is similar to a very familiar process: namely, the need for the parent to behave ever differently toward his growing child.

WHAT IS "GOOD MEDICINE"?

Let us now consider the problem of "good medicine" from the viewpoint of human relationships. The function of sciences is not to tell us what is good or bad but rather to help us understand how things work. "Good" and "bad" are personal judgments, usually decided on the basis of whether or not the object under consideration satisfies us. In viewing the doctor-patient relationship we cannot conclude, however, that anything which satisfies—irrespective of other considerations—is "good." Further complications arise when the method is questioned by which we ascertain whether or not a particular need has been satisfied. Do we take the patient's word for it? Or do we place ourselves into the traditional parental role of "knowing what is best" for our patients (children)?

The shortcomings and dangers inherent in these and in other attempts to clarify some of the most basic aspects of our daily life are too well known to require documentation. It is this very complexity of the situation which has led, as is the rule in scientific work, to an essentially arbitrary simplification of the structure of our field of observation.‡

‡ We omit any discussion of the physician's technical skill, training, equipment, etc. These factors, of course, are of importance, and we do not minimize them. The problem of what is "good medicine" can be considered from a number of viewpoints (e. g., technical skill, economic considerations, social roles, human relationships, etc.). Our scope in this essay is limited to but one—sometimes quite unimportant—aspect of the contact between physician and patient.

Let us present an example. A patient consults a physician because of pain and other symptoms resulting from a duodenal ulcer. Both physician and patient assume that the latter would be better off without these discomforts. The situation now may be structured as follows: healing of the ulcer is "good," whereas its persistence is "bad." What we wish to emphasize is the fact that physician and patient agree (explicitly or otherwise) as to what is good and bad. Without such agreement it is meaningless to speak of a therapeutic relationship.

In other words, the notions of "normal," "abnormal," "symptom," "disease," and the like are social conventions. These definitions often are set by the medical world and are usually tacitly accepted by others. The fact that there is agreement renders it difficult to perceive their changing (and relativistic) character. A brief example will clarify this statement. Some years ago—and among the uneducated even today—fever was regarded as something "bad" ("abnormal," a "symptom"), to be combated. The current scientific opinion is that it is the organism's response to certain types of influences (e. g., infection) and that within limits the manifestation itself should not be "treated."

The issue of agreement is of interest because it has direct bearing on the three models of the doctor-patient relationship. In the first two models "agreement" between physician and patient is taken for granted. The comatose patient obviously can not disagree. According to the second model, the patient does not possess the knowledge to dispute the physician's word. The third category differs in that the physician does not profess to know exactly what is best for the patient. The search for this becomes the essence of the therapeutic interaction. The patient's own experiences furnish indispensable information for eventual agreement, under otherwise favorable circumstances, as to what "health" might be for him.

The characteristics of the different types of doctor-patient relationships are summarized in Table 2. In this connection, some comments will be made on a subject which essentially is philosophical but which continues to plague many medical discussions; namely, the problem of comparing the efficacy of different therapeutic measures. Such comparisons are implicitly based on the following conceptual scheme: We postulate disease "A," from which many patients suffer. Therapies "B," "C," and "D" are given to groups of patients suffering with disease "A," and the results are compared. It is usually overlooked that, for the results to be meaningful, significant conceptual similarities must exist between the operations which are compared. The three categories of the doctor-patient relationship are concretely useful in delineating areas within which meaningful comparisons can be made. Comparisons between therapies belonging to different categories are philosophically (and logically) meaningless and lead to fruitless controversy.

To illustrate this thesis let us consider some examples. A typical comparison, with which we can begin, is that of the various agents used in the treatment of lobar pneumonia: type-specific antisera, sulfonamides, and penicillin. Each superseded the other, as the increased efficacy of the newer preparations was demonstrated. This sort of comparison is meaningful because there is agreement as to what is being treated and as to what constitutes a "successful" result. There should be no need to belabor this point. What is important is that this conceptual model of therapeutic comparisons is constantly used in situations in which it does not apply; that is, in situations in which there is clear-cut disagreement as to what constitutes "cure." In this connection, the problem of peptic ulcer will exemplify a group of illnesses in which several therapeutic approaches are possible.

This question is often posed: Is surgical, medical or psychiatric treatment the "best" for peptic ulcer?§ Unless we specify conditions, goals, and the "price" we are willing to pay (in the largest sense of the word), the

§ Such a question is roughly comparable to asking, "Is an automobile or an airplane better?" —without specifying for what. See Rapoport.[8]

TABLE 2.—*Analysis of the Concepts of "Disease," "Treatment," and "Therapeutic Result"*

Doctor-Patient Relationship	The Meaning of "Treatment"	The "Therapeutic Result"	The Notions of Disease and Health	In Medicine (Illustrative Examples)	In Psychiatry (Illustrative Examples)
1. Activity-passivity	Whatever the physician does; the actual operations (procedures) which he employs	Alteration in the structure and/or function of the patient's body (or behavior, as determined by the physician's judgment); the patient's judgment does not enter into the evaluation of results; e. g., T & A is "successful" irrespective of how patient feels afterward	The presence or absence of some unwanted structure or function The actual state of affairs — The same state without the disability	1. Treatment of the unconscious patient; for example, the patient in diabetic coma; cerebral hemorrhage; shock due to acute injury; etc. 2. Major surgical operation under general anesthesia	1. Hypnosis 2. Convulsive treatments (electroshock, insulin, etc.) 3. Surgical treatments (lobotomy, etc.)
2. Guidance-cooperation	Whatever the physician does; similar to the above	Similar to the above, albeit patient's judgment is no longer completely irrelevant; success of therapy is still the physician's private decision; if patient agrees, he is a good patient, but if he disagrees he is bad or "uncooperative"	The presence or absence of "signs" and "symptoms"; the physician's particular concept of "Disease" (e. g., infection) — "Health" (usually, no disease; e. g., no infection)	Most of general medicine and the postoperative care of surgical patients (e. g., prescription of drugs, "advice" to smoke less, etc.)	1. "Suggestion," counseling, therapy based on "advice," etc. 2. Some modifications of psychoanalytic therapy 3. So-called psychotherapy "combined" with physical therapies (e. g., electric shock)
3. Mutual participation	An abstraction of one aspect of the relationship, embodying the activities of both participants; "treatment" cannot be said to take place unless both participants orient themselves to the task ahead	Much more poorly defined than in the previous models: evaluation of the result will depend on both the physician's and the patient's judgments and is further complicated by the fact that these may change in the very process of treatment	The notions of disease and health lose most of their relevance in this context; the notions of more-or-less successful (for certain purposes) modes of behavior, adaptation, or integration take the place of the earlier, more categorical concepts	The treatment of patients with certain chronic diseases or structural defects; for example, the management of diabetes mellitus or of myasthenia gravis; "rehabilitation" of patients with orthopedic defects, such as learning the use of prostheses, etc.	1. Psychoanalysis 2. Some modifications of psychoanalytic therapy

question is meaningless. In the case of peptic ulcer, it is immediately apparent that each therapeutic approach implies a different conception of "disease" and correspondingly divergent notions of "cure." At the risk of slight overstatement, it can be said that according to the surgical viewpoint the disease is the "lesion," treatment aims at its eradication (by surgical means), and cure consists of its persistent absence (nonrecurrence). If a patient undergoes a vagotomy and all evidence of the lesion disappears, he is considered cured even if he develops another (apparently unrelated) illness six months later. It should be emphasized that no criticism of this frame of reference is intended. The foregoing (surgical) approach is entirely appropriate, and accusations of "narrowness" are no more (nor less) justified than they would be against any other specialized branch of knowledge.

To continue our analysis of therapeutic comparisons, let us consider the same patient (with peptic ulcer) in the hands of an internist. This specialist might have a somewhat different idea of what is wrong with him than did the surgeon. He might regard peptic ulcer as an essentially chronic disease (perhaps due to heredity and other "predispositions"), with which the patient probably will have to live as comfortably as possible for years. This point is emphasized to demonstrate that the surgeon and the internist do not treat the "same disease." How then can the two methods of treatment and their results be compared? The most that can be hoped for is to be able to determine to what extent each method is appropriate and successful within its own frame of reference.

If we take our hypothetical patient to a psychoanalyst, the situation is even more radically different. This specialist will state that he is not treating the "ulcer" and might even go so far as to say that he is not treating the patient for his ulcer. The psychoanalyst (or psychiatrist) has his own ideas about what constitutes "disease," "treatment," and "cure."‖

‖ References 9 and 10.

CONCLUSIONS

Comments have been made on some factors which provide satisfactions to both patient and physician in various therapeutic relationships. In conclusion, we call attention to two important considerations regarding the complementary situations described.

First, it might be thought that one of the three basic models of the doctor-patient relationship is in some fundamental (perhaps ethical) way "better" than another. In particular, it might be considered that it is better to identify with the patient than to treat him like a helplessly sick person. We have tried to avoid such an inference. In our opinion, each of the three types of therapeutic relationship is entirely appropriate under certain circumstances and each is inappropriate under others.

Secondly, we will comment on the therapeutic relationship as a situation (more or less fixed in time) and as a process (leading to change in one or both participants). Most of our previous comments have dealt with the relationship as a situation. It is, however, also a process in that the patient may change not only in terms of his symptoms but also in the way he wishes to relate to his doctor. A typical example is the patient with diabetes mellitus who, when first seen, is in coma. At this time, the relationship must be based on the activity-passivity model. Later, he has to be educated (guided) at the level of cooperation. Finally, ideally, he is treated as a full-fledged partner in the management of his own health (mutual participation). Confronted by a problem of this type, the physician is called upon to change through a corresponding spectrum of attitudes. If he cannot make these changes, he may interfere with the patient's progress and may promote an arrest at some intermediate stage in the evolution toward relative self-management. The other possibility in this situation is that both physician and patient will become dissatisfied with each other. This outcome, however unfortunate, is probably the commonest one. Most of us can probably verify it firsthand in the roles of both physician and patient.[11]

At such juncture, the physician usually feels that the patient is "uncooperative" and "difficult," whereas the patient regards the physician as "unsympathetic" and lacking in understanding of his personally unique needs. Both are correct. Both are confronted by the wish to induce changes in the other. As we well know, this is no easy task. The dilemma is usually resolved when the patient seeks another physician, one who is more attuned to his (new) needs. Conversely, the physician will "seek" a new patient, usually one who will benefit from the physician's (old) needs and corresponding attitudes. And so life goes on.

The pattern described accounts for the familiar fact that patients often choose physicians not solely, or even primarily, on the basis of technical skill. Considerable weight is given to the type of human relationship which they foster. Some patients prefer to be "unconscious" (figuratively speaking), irrespective of what ails them. Others go to the other extreme. The majority probably falls somewhere between these two polar opposites. Physicians, motivated by similar personal "conflicts" form a complementary series. Thus, there is an interlocking integration of the sick and his healer.

SUMMARY

The introduction of the construct of "human relationship" represents an addition to the repertoire of fundamental medical concepts.

Three basic models of the doctor-patient relationship are described with examples. The models are (*a*) Activity-passivity. The comatose patient is completely helpless. The physician must take over and do something to him. (*b*) Guidance-cooperation. The patient with an acute infectious process seeks help and is ready and willing to cooperate. He turns to the physician for guidance. (*c*) Mutual participation. The patient with a chronic disease is aided to help himself.

The physician's own inner needs (and satisfactions) form a complementary series with those of the patient.

The general problem usually referred to with the question "what is good medicine?" is briefly considered. Different types of doctor-patient relationships imply different concepts of "disease," "treatment," and "cure." This is of importance in comparing diverse therapeutic methods. Meaningful comparisons can be made only if interventions are based on the same frame of reference.

It has been emphasized that different types of doctor-patient relationships are necessary and appropriate for various circumstances. Problems in human contact between physician and patient often arise if in the course of treatment changes require an alteration in the pattern of the doctor-patient relationship. This may lead to a dissolution of the relationship.

REFERENCES

1. Ruesch, J., and Bateson, G.: Communication: The Social Matrix of Psychiatry, New York, W. W. Norton & Company, Inc., 1951.

2. Dewey, J., and Bentley, A. F.: Knowing and the Known, Boston, Beacon Press, 1949.

3. Russell, B.: Power: A New Social Analysis, New York, W. W. Norton & Company, Inc., 1938.

4. Szasz, T. S.: Entropy, Organization, and the Problem of the Economy of Human Relationships, Internat. J. Psychoanal. **36**:289, 1955.

5. Dubos, R. J.: Second Thoughts on the Germ Theory, Scient. Am. **192**:31, 1955.

6. Jones, E.: The God Complex, in Jones E.: Essays in Applied Psychoanalysis, London, Hogarth Press, 1951, Vol. 2, p. 244.

7. Marmor, J.: The Feeling of Superiority: An Occupational Hazard in the Practice of Psychotherapy, Am. J. Psychiat. **110**:370, 1953.

8. Rapoport, A.: Operational Philosophy, New York, Harper & Brothers, 1954.

9. Zilboorg, G.: A History of Medical Psychology, New York, W. W. Norton & Company, Inc., 1941.

10. Bowman, K. M., and Rose, M.: Do Our Medical Colleagues Know What to Expect from Psychotherapy? Am. J. Psychiat. **111**:401, 1954.

11. Pinner, M., and Miller, B. F., Editors: When Doctors Are Patients, New York, W. W. Norton & Company, Inc., 1952.

Primary Atypical Nonbacterial Pneumonia

An Evaluation of the Efficacy of Antibiotic Therapy in One Hundred Eighteen Cases

LT. ROBERT L. WOLF (MC), U.S.N.R.
and
CMDR. LOY T. BROWN (MC), U.S.N.,

INTRODUCTION

Primary atypical nonbacterial pneumonia has emerged from relative obscurity to particular prominence during the past 20 years.* Despite the increased frequency with which this disease is now recognized, there have been few large published series with adequate controls and serial clinical and laboratory studies which evaluate the efficacy of the various therapeutic agents presently available. The opportunity to evaluate critically the therapeutic effect of various antibiotics in a large population of patients with primary atypical nonbacterial pneumonia is infrequently available.[4] These populations, however, occasionally occur when large numbers of people congregate in military installations. Unbiased sampling of a large population of patients with primary atypical nonbacterial pneumonia may be undertaken, under these conditions.

In the year 1812, cases of pneumonitis identical in both clinical and pathological description to primary atypical nonbacterial pneumonia were first described.[5] Little attention was given to the disease until 1934, when disparity between the physical signs and roentgenologic findings in cases of "bronchopneumonia" in youths was first emphasized.[6] During World War II a Commission on Acute Respiratory Diseases was organized to investigate this disorder, and the findings of that group have greatly increased our knowledge.[7] Little is known, however, concerning the causative agents or the effectiveness of the various antibiotics presently available.

Preliminary studies on the pulmonary disease ward of the United States Naval Hospital, Bainbridge, Md., disclosed that the majority of patients with pneumonitis had primary atypical nonbacterial pneumonia. Furthermore, although several other investigators have not had similar experiences, our preliminary investigation yielded the impression that the currently available antibiotics did not alter the course of the disease.† Many of the published reports analyzed the clinical response in treated and untreated patients, using the duration of fever and clinical symptoms for comparison. Frequently the reported series was inadequately controlled. Since the disease is variable with respect to duration of clinical symptoms, fever, physical findings, abnormal laboratory results, and pulmonary infiltrations as determined by roentgenograms, it is apparent that adequate studies and valid conclusions can be made only when comparable groups of treated and untreated patients are employed with use of all these methods of evaluation.

To confirm our preliminary impressions, the present study was organized. It is the purpose of this paper to report a statistical evaluation of observations made on 118 consecutive patients who had primary atypical nonbacterial pneumonia. This planned study includes four groups of patients treated with

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From the Departments of Pathology and Radiology, U. S. Naval Hospital, Bainbridge, Md.

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* References 1-3.

† References 4 and 8-12.

various antibiotics. They were compared with a control group which received no specific treatment. All patients had similar serial, clinical, laboratory, and roentgenologic examinations. Investigations were also performed to correlate the incidence of hemolytic anemia with primary atypical nonbacterial pneumonia and cold isohemagglutinins.

MATERIALS AND METHODS

During the period July 15, 1954, to March 31, 1955, there was a total of 205 patients admitted to the pulmonary disease ward of this hospital. Of these 205 patients, 118 fulfilled the criteria for the diagnosis of primary atypical nonbacterial pneumonia. These patients were the subjects for our investigation.

The criteria for the diagnosis of primary atypical nonbacterial pneumonia were identical with those of other investigators.‡ The fundamental features were the following:

1. Clinical history of respiratory tract disease characterized by gradual onset, cough, fever, chilly sensations, and, occasionally, substernal pain, usually without hemoptysis, abrupt onset, or an initial chill.
2. Physical examination which frequently disclosed a disparity between the minimal pulmonary physical signs and the extent of pulmonary involvement exhibited by roentgenograms.
3. Roentgenologic evidence of pulmonary parenchymal disease.
4. Absence of cultural or serological evidence of known bacterial or viral agents in the etiology of the disease.

Since there are probably several unknown causative agents acting separately or synergistically in the production of this disease, there are presently no specific diagnostic tests, although the test for cold isohemagglutinins occasionally may be of value.

All of the patients included in this investigation were young males. The age range was 17 to 36 years, with a mean of 18.6 years. At the time of admission to the pulmonary disease ward the patients were randomly placed into one of five groups for the purpose of this investigation. The groups were named in conformity with the therapy received as follows:

Group 1. No specific therapy
Group 2. Chlortetracycline hydrochloride therapy
Group 3. Erythromycin stearate therapy
Group 4. Oxytetracycline hydrochloride therapy
Group 5. Tetracycline hydrochloride therapy.

‡ References 1, 3, 4, 8, and 9.

All the patients were treated identically except for the variation in antibiotic therapy. The patients were confined to bed and received the routine hospital diet. No antipyretics were used. Several patients were given aqueous phenylephrine (Neo-Synephrine) nose drops and a cough preparation containing terpin hydrate elixir. The only variation in treatment was in the antibiotic employed. Group 1 received no antibiotic. Groups 2, 4, and 5 received chlortetracycline hydrochloride, oxytetracycline hydrochloride, and tetracycline hydrochloride, respectively, in doses of 500 mg. by mouth every six hours. Group 3 received erythromycin stearate in doses of 400 mg. by mouth every six hours. The dosage of antibiotic employed was arbitrarily selected.

The mean day of the disease on which therapy was initiated was 5.3. There was no significant difference in the interval of time between the onset of the disease and the institution of therapy in any of the groups. Antibiotic therapy was continued in Groups 2, 3, 4, and 5 until the first chest roentgenogram did not reveal any pulmonary parenchymal lesions.

The history and physical examination findings were recorded on admission to the hospital on a standard form symptom and sign check sheet, and this was repeated as frequently as clinically indicated and at weekly intervals.

The following laboratory studies, with use of the standard procedures, were performed upon admission and at weekly intervals thereafter:

Hematology: Complete blood study, including hematocrit value and sedimentation rate (Wintrobe-Landsberg method).

Urinalysis: Routine urinalysis, including determination of bilirubin (Harrison spot test) and urobilinogen (Wallace and Diamond method).

Bacteriology: Both sputum specimens and nose and throat swabs studied by Gram and Ziehl-Neelsen stains and culture on ordinary and Dubos media.

Serology: Cold isohemagglutinins, heterophile antibody, and direct Coombs test. Serologic tests were also performed on several randomly selected patients for the antibodies associated with infection produced by the influenza virus and psittacosis and for agglutinins produced by the enteric group, Brucella tularensis, Proteus OX19, and Proteus OX2. The strains of influenza virus employed were Types A(PR-8), A′ (FM-1), B(1B-1), and B(Lee).

Posteroanterior chest films were made of each of the 118 subjects on admission to the hospital. All films demonstrated definite parenchymal lesions. Thereafter roentgenograms of the chest were made at five- to ten-day intervals, the majority exactly weekly. When indicated for more precise localization of a lesion, the proper lateral or oblique roentgenogram was made.

RESULTS

Most of the patients with the diagnosis of primary atypical nonbacterial pneumonia had clinical symptoms and physical signs compatible with the disease. A few of the patients were clinically asymptomatic and the presence of pneumonitis was discovered on routine roentgenologic chest examination. Bacteriologic examination of both sputum specimens and nose and throat swabs did not reveal a predominance of any of the pathogenic organisms commonly associated with pneumonia. Rising titers, or titers of 1 : 32 or higher, of cold isohemagglutinins were present in the serum of 56% of the patients. None of the patients had a heterophile antibody titer of 1 : 28 or higher. No significant rise in titer of the agglutinins associated with disease produced by the influenza virus, psittacosis, enteric group, B. tularensis, Proteus OX19, and Proteus OX2 was demonstrated.

The hemoglobin values, hematocrit values, and red blood cell counts were normal upon admission and throughout the disease in all of the patients. In all of the patients the direct Coombs test was negative. There was no bilirubin in the urine, and the urinary urobilinogen titer was always between 1 : 8 and 1 : 32. All of the patients, therefore, fulfilled the criteria for primary atypical nonbacterial pneumonia, and none of them developed any evidence of hemolytic anemia.

The number of patients in each of the five groups was as follows: Group 1, 44 patients; Group 2, 21 patients; Group 3, 15 patients; Group 4, 11 patients, and Group 5, 30 patients. The course of the disease was statistically studied in control Group 1 and Groups 2, 3, 4, and 5 by comparing the duration of the following abnormal findings: temperature of 100 F or higher, white blood cell counts greater than 10,000 cells/cu. mm., erythrocyte sedimentation rates greater than 10 mm. in one hour, elevated cold isohemagglutination titers, and roentgenologic evidence of pneumonitis.

No significant difference was present between control Group 1 and Groups 2, 3, 4, and 5 in the comparison of duration of white blood cell counts greater than 10,000 cells/cu. mm., elevated erythrocyte sedimentation rates, and elevated isohemagglutination titers. The value of P in each of these instances was >0.05.

The Table summarizes the statistics for comparison of control Group 1 and Groups 2, 3, 4, and 5 regarding the duration of fever and pneumonitis. A significant increase in the duration of fever of the patients treated with chlortetracycline hydrochloride and erythromycin stearate was observed when comparison was made with the patients who received no antibiotic therapy. The P value in each of these instances was <0.05. There was no significant difference in the duration of fever between the patients in control Group 1 and the patients in Groups 4 and 5, who received oxytetracycline hydrochloride and tetracycline hydrochloride, respectively. The P values for these groups were both >0.05.

Three patients in Group 2, who were treated with chlortetracycline hydrochloride, had a duration of pneumonitis determined by roentgenologic examination of 11, 9, and 8 weeks, respectively. The mean duration of

Summary of Statistics for Comparison of Four Groups of Patients with Primary Atypical Nonbacterial Pneumonia Treated with Antibiotics and a Control Group of Patients with Primary Atypical Nonbacterial Pneumonia Treated Without Antibiotics

Group	Antibiotic	Duration of Fever (100 F), Days			Duration of Pneumonitis (Determined by Roentgenologic Examination), Wk.		
		$\bar{x}$	t	P	$\bar{x}$	t	P
1	None	0.8			2.3		
2	Chlortetracycline hydrochloride	1.8	2.38	<0.05	2.4	0.035	>0.05
3	Erythromycin stearate	2.3	3.11	<0.05	2.2	1.05	>0.05
4	Oxytetracycline hydrochloride	1.3	0.90	>0.05	2.6	0.73	>0.05
5	Tetracycline hydrochloride	1.3	1.41	>0.05	2.4	0.033	>0.05

pneumonitis determined by roentgenologic examinations in the remaining 19 patients was 2.4 weeks. Since the duration of pneumonitis in these three patients was greater than the mean duration of pneumonitis plus three standard deviations ($2.4+[3\times0.8]$) of the remaining 19 patients, they were considered biased and were deleted from the calculations of this group.

A comparison of the patients treated with chlortetracycline hydrochloride, erythromycin stearate, oxytetracycline hydrochloride, and tetracycline hydrochloride with those patients who had no antibiotic therapy did not reveal any increase in the duration of pneumonitis ($P>0.05$).

In general, the roentgenologic findings in the 118 patients corresponded well with those reported by other investigators both in type and distribution of the pathologic process.§ A "patchy" form of distribution was encountered in 9 cases (7.6%), and an interstitial or peribronchial type, in 81 cases (68.6%). Both forms together were observed in 34 cases (28.8%). Sharply localized lobar involvement was seen in seven instances (5.9%). Of the latter, the right middle lobe was most frequently diseased (four cases). The right upper lobe was involved in two cases, and in one instance both right middle and right lower lobes were involved. It was noted, however, that in no instance was the infiltrate of the obliterating density expected with lobar bacterial pneumonia. Clear-cut segmental localization was evident only in two cases, when lower lobe segments were involved in the disease process.

The frequency of parenchymal involvement by lobes followed the pattern ordinarily noted in that lower lobe disease predominated. However, in this series, lower lobe infiltration was more commonly encountered on the left than on the right, a finding which disagrees with that noted by Reich, who found right lower lobe disease predominant.[18] In this study the right upper lobe was the seat of activity in 9 cases (7.6%); the right middle lobe, in 13 cases (11.0%), and the right lower lobe, in 49 cases (41.5%). The left upper lobe was involved in 5 subjects (4.2%), and the left lower lobe, in 80 patients (67.8%). Multiple lobes in one lung presented evidence of disease in seven cases (5.9%). Both lungs demonstrated parenchymal infiltration in 19 patients (16.1%), and, of these, 4 cases had three or four lobes involved in the disease process. Of those patients presenting disease in both lungs, the lower lobe pair was most commonly active in the pneumonic process, 17 cases showing both right and left lower lobe activity.

Evidence of hilar enlargement from lymphadenopathy was not noted except in three instances. The usual roentgenographic findings seen with extensive obstructive atelectasis (mediastinal shift, elevation of the diaphragm, and narrowing of the intercostal spaces) were not observed. One case, however, did present evidence of discoid atelectasis in the resolving phase of the disease.

Nine patients, or 7.6% of the total number, either initially presented or later developed roentgenographic signs of pleural effusion. One of these demonstrated bilateral pleural effusions. In no instance was the pleural effusion of an extent great enough to warrant thoracentesis. There were no complications.

COMMENT

Comparison of the treated and untreated groups is justified by the almost identical age, sex, duration of illness prior to the initiation of therapy, and severity of clinical symptoms and physical signs.

There was no significant difference in duration of elevated white blood cell counts, elevated erythrocyte sedimentation rates, and elevated cold isohemagglutination titers in the treated and untreated groups. Although these differences were not significant, the mean duration of elevated white blood cell counts in all of the groups treated with antibiotics, the mean duration of elevated erythrocyte sedimentation rates in Group 4, and the mean duration of elevated cold isohemagglutination titers in Groups 3 and 4 were

§ References 1, 16, and 17.

less than in the control Group 1. Moreover, there was no significant difference in the duration of fever between the untreated control Group 1 and Groups 4 and 5 which received antibiotic therapy. Considering all of these factors, the control Group 1 probably contained patients with primary atypical nonbacterial pneumonia of equal or greater severity than the treated groups, and this would tend to magnify any presumed beneficial effect of the antibiotics in the treated groups.

There was no significant difference in the duration of roentgenologically demonstrated pneumonitis in the antibiotic-treated patients of Groups 2, 3, 4, and 5 compared with the untreated control Group 1. In reviewing the films of the entire series it was evident that no single group of cases included persons with a higher proportion of the more severe pneumonias, as shown by the number of involved lobes, the quantity of diseased lung tissue, or by the presence of pleural effusion. The review also indicated that the method of treatment had no influence on the manner of resolution. Patients of each group presented similar gradual clearing of the infiltrative process on the frequent follow-up films.

Although the mean duration of fever was significantly greater in the antibiotic-treated Groups 2 and 3 in comparison with the control Group 1, there was no significant difference between Groups 2 and 3 compared with control Group 1 in duration of elevated white blood cell counts, elevated erythrocyte sedimentation rates, elevated cold isohemagglutination titers, and duration of pneumonitis as determined by roentgenologic examination. Consequently, the difference in the duration of fever in Groups 2 and 3 compared with the control Group 1 is presumed to be related to the variability of the disease and not to the therapy which the patients received.

This evaluation indicates that chlortetracycline hydrochloride, erythromycin stearate, oxytetracycline hydrochloride, and tetracycline hydrochloride do not alter the duration of pneumonitis in primary atypical nonbacterial pneumonia. Similarly, Walker [13] demonstrated that chlortetracycline hydrochloride is without effect upon the manifestations of the disease in the pulmonary parenchyma. Homer and co-workers [14] conclude that chlortetracycline hydrochloride and oxytetracycline hydrochloride have no effect on the duration of pneumonitis in primary atypical nonbacterial pneumonia.

Although other investigators state that chlortetracycline hydrochloride and oxytetracycline hydrochloride are effective in the clinical treatment of this disease in man and even inhibit the development of pneumonitis in cotton rats inoculated with a virus obtained from patients with primary atypical nonbacterial pneumonia, clinical practice has not always substantiated these claims.‖ These studies demonstrate the ineffectiveness of the four antibiotics employed in influencing the duration of pneumonitis in primary atypical nonbacterial pneumonia.

SUMMARY

Four groups of patients with primary atypical nonbacterial pneumonia were treated with chlortetracycline hydrochloride, erythromycin stearate, oxytetracycline hydrochloride, and tetracycline hydrochloride, respectively. These patients were compared with a control group of patients with primary atypical nonbacterial pneumonia who received no specific therapy. The results indicate that the antibiotics employed do not alter the duration of pneumonitis in primary atypical nonbacterial pneumonia.

REFERENCES

1. Reimann, H. A.: The Viral Pneumonias and Pneumonias of Probable Viral Origin, Medicine **26**:167-219 (March) 1947.

2. Chang, H. T.: Studies on Primary Atypical Pneumonia in Peking: 1. Clinical Analysis of 42 Cases and the Report of a Case with Neurological Complication, Chinese M. J. **69**:455-469 (Nov.-Dec.) 1951.

3. Jordan, W. S.; Albright, R. W.; McCain, F. H., and Dingle, J. H.: Clinical Variations in Primary Atypical Pneumonia, Am. J. Med. **10**:3-20 (Jan.) 1951.

‖ References 4, 5, 8, 9, 11, and 15.

4. Schoenbach, E. B.; Sweed, A.; Tepper, B., and Bryer, M. S.: An Evaluation of Aureomycin Therapy in Primary Atypical Pneumonia, New England J. Med. **243**:799-806 (Nov. 23) 1950.

5. Dingle, J. H., and Finland, M.: Virus Pneumonias: II. Primary Atypical Pneumonia of Unknown Etiology, New England J. Med. **227**:378-385 (Sept. 3) 1942.

6. Gallagher, J. R.: Bronchopneumonia in Adolescence, Yale J. Biol. & Med. **7**:23-40 (Oct.) 1934.

7. Commission on Acute Respiratory Diseases: Primary Atypical Pneumonia, Am. J. Pub. Health **34**:347-357 (April) 1944.

8. Finland, M.; Collins, H. S., and Wells, E. B.: Aureomycin in the Treatment of Primary Atypical Pneumonia, New England J. Med. **240**:241-246 (Feb. 17) 1949.

9. Schoenbach, E. B., and Bryer, M. S.: Treatment of Primary Atypical Nonbacterial Pneumonia with Aureomycin, J. A. M. A. **139**:275-280 (Jan. 29) 1949.

10. Cameron, I. G.: Chloromycetin and Primary Atypical Pneumonia, East African M. J. **27**:243 (June) 1950.

11. Graves, F. B., and Ball, W. O.: Evaluation of the Treatment of Primary Atypical Pneumonia with Aureomycin, Chloromycetin and Terramycin, J. Pediat. **39**:155-167 (Aug.) 1951.

12. Auerbach, S. H.; Mins, O. M., and Goodpasture, E. W.: Pulmonary Fibrosis Secondary to Pneumonia, Am. J. Path. **28**:69-87 (Jan.-Feb.) 1952.

13. Walker, S. H.: Ineffectiveness of Aureomycin in Primary Atypical Pneumonia, Am. J. Med. **15**: 593-602 (Nov.) 1953.

14. Homer, L.; Donovan, W. H., and Radke, R. A.: Effect of Antibiotics in Abacterial Pneumonia, U. S. Armed Forces M. J. **3**:1767-1775 (Dec.) 1952.

15. Eaton, M. D.: Action of Aureomycin and Chloromycetin on the Virus of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **73**:24-29 (Jan.) 1950.

16. Syverton, J. T.: Non-Bacterial Pneumonias, Dis. Chest **18**:456-477 (Nov.) 1950.

17. Sante, L. R.: Roentgenologic Findings in Atypical Pneumonia, Mississippi Valley M. J. **69**: 70-72 (April) 1947.

18. Reich, N. E.; Ciarolo, L. F., and Reinhart, J. B.: Primary Atypical Pneumonia: The Diagnosis and Treatment of 440 Consecutive Cases Without a Fatality, Am. Pract. **2**:85-98 (Oct.) 1947.

Treatment in Internal Medicine

RECOGNITION AND TREATMENT OF THE VARIOUS SEIZURE DISORDERS IN MEDICAL PRACTICE

LEWIS LEVY, M.D.
and
EDWARD SHANBROM, M.D., New Haven, Conn.

WHEN THE term "epilepsy" is mentioned, physician and layman alike immediately conjure up the familiar picture of a gross convulsion. Although grand mal epilepsy is the most obvious of the seizure disorders, there is a greater number of attacks which may never manifest themselves as typical "fits." Awareness of the variability of epileptic conditions and their management is of the utmost importance to all physicians, since recognition of the disease may save the patient needless examinations and laboratory studies and correct treatment will prevent progressive damage to the central nervous system. It is the purpose of this paper to discuss the various forms of epilepsy, with special emphasis on those ictal states which may be mistaken for other medical diseases.

INCIDENCE

It is difficult to estimate the true incidence of the epileptic states, since there are unquestionably a very large number of patients who have unrecognized seizures or who never seek medical help. Some idea of the magnitude of the epileptic problem is gained from a statement by William Lennox: "Epilepsy constitutes something like 10% of the Nation's neuropsychiatric burden." [1] According to the American Branch of the International League Against Epilepsy, the estimated rate of known epilepsy in this country is 1 in 200; other estimates are as high as 1,500,000 persons. It is further estimated that 1 out of 10 persons has a dysrhythmic electroencephalogram, and some of these patients may have unrecognized seizures. With the exception of heart disease, then, there are few chronic illnesses commoner than epilepsy for which we can offer specific therapy.

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From the Section of Neurology and Medical Service, Veterans Administration Hospital. Assistant Clinical Professor, Neurology, Yale University School of Medicine (Dr. Levy); present address: Department of Medicine, Yale University School of Medicine (Dr. Shanbrom).

ETIOLOGY

In general, two forms of epilepsy are recognized, primary, or idiopathic, and secondary. The primary epilepsies are the commonest. Many theories have been advanced concerning the etiology of this form of the disease, but, to date, none can be fully accepted. Many pathologists have demonstrated fairly distinct lesions in the brains of these patients in the form of glial proliferations, but it is the feeling of others that such changes may well result from the seizures themselves, which are associated with changes in blood flow and metabolic activity. It is probable that primary epilepsy is the result of biochemical rather than structural changes in cerebral tissue, but a great deal more work remains to be done in this field. Heredity seems to be a definite factor.

Secondary epilepsy results from specific structural changes within the brain and may be associated with a variety of pathologic conditions, including infection, neoplasm, trauma, and vascular, metabolic, and degenerative diseases. Obviously, it is important to diagnose the cause correctly in secondary epilepsy so that the more specific therapeutic measures may be instituted, but, as will be pointed out later in the article, many of these cases may be handled in the same fashion as the idiopathic group.

CLASSIFICATION

It is difficult to present a completely satisfactory classification of the epilepsies. Many

neurologists have divided them into two main groups, generalized and partial, on the basis of the clinical and electroencephalographic manifestations. For the most part we have followed the plan of classification of Gastaut.[2]

A. Generalized Epilepsy.—These seizures are manifested clinically by loss of consciousness (not simply altered states of awareness, as may occur in partial epilepsies) and electrographically by bilateral seizure discharges from both cerebral hemispheres during the convulsion.

1. Grand Mal: These states are familiar to all physicians. They begin with sudden loss of consciousness. The patient falls to the ground and becomes rigid. In a few seconds there begins a generalized trembling, which increases in intensity and develops into intense clonic jerks. There may be loss of control of bladder and rectum, frothing at the mouth, tongue biting, cyanosis, and gnashing of the lips and tongue. As the convulsion ends, muscles relax and consciousness returns. The whole episode lasts about five or six minutes. A period of confusion and disorientation or extreme motor activity lasting several minutes or a few hours, frequently generalized throbbing headache, and a period of sleep may follow the seizure.

2. Petit Mal: True petit mal seizures are seen in childhood and practically never occur in adult life. Many cases diagnosed as petit mal are actually partial epilepsy of the psychomotor type. The attack occurs as a very brief loss of consciousness, during which time the child is completely unaware of his surroundings. He may stop in the middle of a sentence, stare blankly ahead, and remain fixed and immobile. He may appear pale, and there may be an upward rolling of the eyes. Sometimes the eyelids and muscles of the extremities exhibit extremely fine slow rhythmic jerks. As soon as the seizure ends, he resumes activity where it has been left off, often without realizing that anything has happened. These attacks characteristically occur many times a day (5 to 100), last less than 20 seconds, and may be so brief as to be imperceptible to an untrained spectator. They appear simply as a "lapse" in which the child hesitates carrying out some motor activity or intellectual function. These latter forms are important to recognize, since they interfere with a child's educational activities and cause undue psychic trauma as he is accused of being a "day-dreamer."

B. Partial Epilepsy.—These seizures have also been referred to as "focal" or "local" seizures. The entire clinical picture depends on the area of the brain which is involved in the seizure activity. They occur without loss of consciousness, although the patient may exhibit an altered state of awareness. Originally, only disturbances of the motor system were recognized in this form of epilepsy, for the symptoms produced by stimulation of the motor cortex, such as the jerking of an extremity, are obvious. Eventually disorders of sensory, autonomic, and psychical sectors of the brain have been recognized, and it is these ictal states which give rise to the most unusual and bizarre clinical pictures. Even though partial seizures begin in a localized area in the cortex, the electrical activity may spread to adjacent areas of brain or to the opposite cortex, so that the symptoms may change, depending on the area of the brain taking part in the seizure discharge. Thus, a seizure may begin in a sensory area and spread to the motor cortex, producing clonic jerks of the extremities. Further, although an attack may begin in a localized fashion, it may spread to involve the entire cortex and end in a generalized convulsion. Following the epileptic attack itself a postictal state may occur similar to that following a grand mal seizure. The electrographic picture is variable in the partial epilepsies. There may be seizure discharges on one side of the head and localized in one specific area, or there may be diffuse and bilateral activity; when the discharge is bilateral it may predominate on one side.

1. Motor Seizures: Motor seizures originate in the prerolandic area (precentral gyrus) of the frontal lobe. The motor speech area in the dominant hemisphere may give

rise to aphasic seizures, while the center for conjugate deviations of head and eyes is involved in versive seizures, as will be described.

(*a*) Clonic type. Also called "focal motor," these seizures are characterized by rhythmic jerking of a portion of one side of the body. Most commonly the upper extremities, head, face, corner of the mouth, and eyelids are involved, but occasionally the seizure may spread to adjacent areas of the body in the so-called "Jacksonian march." The explanation for the pattern of the spread of the seizure is to be found in the representation of the body in the precentral gyrus ("motor strip"), as originally described by Hughlings Jackson and later confirmed by Penfield.[8] In the periods between the obvious seizures some of these patients may have isolated clonic twitches confined to one area of the body. This condition may severely handicap the patient if it involves his hand or may present a rather bizarre or confusing picture to the physician if he fails to recognize the rest of the epileptic picture.

A 22-year-old white man complained of episodes of tingling in his right arm and hand lasting five minutes. Attacks recurred weekly over a period of 10 months. Jerking of his right arm and leg was observed during an episode which progressed to coma. Following this attack he began to have episodes of flexion of his right hand and arm which would last about 5 to 10 minutes, preceded by 1 minute of numbness of the extremity. Following antiepileptic therapy the seizures stopped, but the patient had residual weakness of the right hand. Air studies and arteriography failed to reveal evidence of tumor.

This case illustrates the fact that somatomotor seizures may occasionally be followed by paralysis and emphasizes the need for adequate antiepileptic therapy.

(*b*) Tonic type. These consist of spasm of extensor or flexor muscle groups, and the clinical picture will depend on which group predominates. Thus, in a tonic seizure of the extensor muscles the patient may appear to be stretching himself as far as he can and even assume the position of opisthotonos. If the seizures are severe and frequent it may cause the physician to consider the diagnosis of tetanus seriously. If the flexor muscles are involved, the patient will appear to curl up.

A 34-year-old white man received a severe head injury when his ship was torpedoed during the war. About two weeks after the injury he began to have episodes of tingling in the fingers of the right hand followed by loss of consciousness, during which time he would be seen to clench his jaw, stretch all extremities until they were rigid, and arch his back and neck. Following an attack the patient became somnolent for a period of time varying from a few minutes to an hour.

(*c*) Versive type. These consist of turning of the eyes, head, and body to one side. The turning motion always develops progressively from the head down to the body, although the eyes or head alone may be involved, depending on the extent of spread of the seizure discharge. The action may be sporadic or continuous. These movements arise in the premotor portion of the frontal lobe.

2. Aphasic Seizures: These arise from the speech areas of the "dominant" hemisphere. They may consist simply of arrested speech, wherein the patient is aware that he cannot utter the word he desires to, or they may be more complex, in that the patient is unable to find the words to express himself. Usually this is part of a more diffuse focal seizure with other motor or sensory components.

A 27-year-old white man described the following attack while aboard ship en route to Korea. "I arose from my desk for a glass of water. I glanced at my face in the mirror and suddenly a mental picture grasped my attention. Thinking I recognized it, I attempted to remember what it was. Immediately I felt a buzzing in my head. I stumbled back into my room, sat down in my chair and put my head between my knees feeling as if I would faint. Some of my friends saw that something was wrong with me and proceeded to help me back to my bed. I was unable to speak or communicate with them in any way although I was perfectly aware that they were trying to help me."

3. Sensory Seizures: (*a*) Somatosensory type. These seizures originate in the parietal lobe. The sensory representation of the body on the postcentral gyrus has been well described by Penfield and Rasmussen.[8] The

patient may complain of peculiar sensations such as warmth, cold, numbness, tingling, or abnormal positions of one part of the body in relation to the rest. These sensations may be confined to one area of the body or spread to involve adjacent areas and the entire side of the body. In some patients an attack may be triggered off by stimulation of the part of the body that is usually involved in the seizure, such as a sudden blow to an extremity. This form of epilepsy is frequently mistaken for hysterical fits.

A 32-year-old white male electrician had the following type of seizure: There was a sudden sensation of numbness or tingling beginning in the right hand. The numbness would extend rapidly up to the wrist and arm, and about the same time he noticed numbness beginning in the right side of his face in the area of the cheek and lips. The numbness would then spread to involve the entire shoulder, head, neck, and trunk, and would then travel down the right lower extremity to involve his toes. Finally, there was a peculiar sensation deep within the abdomen, and the patient felt nauseated and frequently would vomit. At this point he could not speak. Following the spell he had a severe generalized throbbing headache which lasted for a few hours to a few days.

(*b*) Seizures of special senses. Depending on the area of the cortex which is stimulated, there may be abnormal sensations of vision, smell, taste, hearing, and balance. Here, too, the bizarre nature of the patient's complaints and their evanescent character either bewilders the unsuspecting physician or suggests to him the diagnosis of a hysterical reaction.

A 34-year-old housewife described the following attack. There was a ringing in the ears which was followed by a hollow sound, as if she were in an auditorium. This was then followed by a repetition of a song which appeared to mimic all the noises of factory machines. Some of these attacks were followed by grand mal convulsions.

(*c*) Psychic seizures.* These seizures are considerably commoner than is generally realized. When they occur as part of a general epileptic attack they are easily recognized, but if they occur as isolated seizures in themselves, they may be undiagnosed. The seizures take the form of hallucinations, illusions, compulsive ideas, or changes in moods. The hallucinations are like dreams and usually present the same picture with each attack. Illusions may refer to changes in the size of objects near at hand, or they may simply consist of the peculiar sensation of reexperiencing a situation as if it had previously occurred (déjà vu phenomenon), or the opposite feeling may be present, in which the patient fails to recognize objects, faces, or places no matter how familiar they actually are (jamais vu). The latter sensation differs from another illusion in which the patient has a feeling of unreality, as if he were in a dream, and feels completely removed from his immediate surroundings. Compulsive ideas and sudden mood changes usually present as brief intrusions into the patient's consciousness. He may exhibit sudden anxiety or fear, or, on the other hand, may experience a remarkable feeling of happiness. The relationship of epilepsy to personality and emotions has been very well reviewed by Denis Williams.[4]

CASE 1.—A 22-year-old white male gas-station attendant had attacks manifested by a feeling of fear which was gradually replaced by negative and hostile behavior lasting about 30 minutes. During this time he appeared dazed. Following the episode there was amnesia and the patient had a severe hatband-like headache. An electroencephalogram was diffusely abnormal, showing random spike activity.

CASE 2.—A young college graduate wrote the following description during one of his attacks: "For two to four minutes my mind left this world and I was possessed with a new reason with which I could explain nothing, but which grasped me with the idea that I was indeed in a new world of reason. My mind was way up in the stratosphere. Upon release from it, I was simply crushed with complete loss of confidence in my mental picture. Upon return to a rational state I could not remember my name for fifteen to thirty minutes."

4. Automatisms: These are probably more frequent than is realized, and the symptoms may be extremely varied. They consist of motor activities varying from a simple nonsensical gesture to a more complicated ambulatory automatism, in which the patient

* Psychic seizures and the seizures to be described below (automatisms and visceral seizures) are generally referred to as "psychomotor seizures."

wanders about not realizing he has changed from his previously determined destination. They may consist of sudden emotional outbursts of anger, fear, depression, or hilarity. Other automatisms may be manifested by peculiar movements of the oral cavities such as smacking of the lips, chewing, or swallowing or by picking or stroking clothes and parts of the body. Finally, the patient may manifest a verbal automatism, mumbling unintelligibly or crying out some trite phrase. Gastaut [5] has outlined a striking similarity between the results of rhinencephalic stimulation in animals and human psychomotor seizures and between the similarities of interseizure behavior in animals with rhinencephalic epileptogenic scars and humans with psychomotor epilepsy. This and other work [6] on the so-called "visceral brain" clearly implicates these structures in the mechanism of psychic seizures and suggests a neuroanatomic basis of behavior.

CASE 1.—A 45-year-old pipefitter bought an ice cream cone in midtown New York. He began to eat the ice cream and thereafter found himself several blocks away, with his clothes disheveled, still holding the ice cream cone in his hand but noticed that the ice cream had melted away. He had amnesia for the entire episode.

CASE 2.—A 35-year-old housewife had the following seizure prior to the removal of a right temporal lobe astrocytoma: Standing in the office of her physician, she suddenly stared straight ahead with a silly grin on her face. When her physician tried to help her into a chair, her body stiffened and she pulled at his hands. Once seated she picked at her clothes, pulled off her slippers, and gradually seemed to become aware of her surroundings. She had amnesia for the entire episode. When asked, she estimated that about 10 minutes had elapsed. According to the physician, the entire episode took place in only 20 or 30 seconds.

5. "Visceral" seizures: This form of epilepsy is the most perplexing to the internist, but awareness of the existence of this condition may help to solve many diagnostic problems and avert the expense of repeated laboratory studies. An extensive report of visceral epilepsy was written by Mulder, Daly, and Bailey,[7] in which 100 cases were reviewed. The reader is referred to this paper for a more comprehensive study and description of the clinical picture. Symptoms may be referred to any of the viscera. Gastrointestinal symptoms may appear as a "lump in the throat," epigastric burning or pain, intestinal cramps, nausea, or a general weakness in the "pit of my stomach." Seizures associated with cardiorespiratory symptoms may present precordial pain suggestive of angina, palpations, tachycardia, dyspnea, hyperventilation, or a sensation of suffocation. Actual cardiac arrhythmias have been ascribed to visceral epileptic attacks.[8] Many visceral seizures are accompanied by symptoms of autonomic disturbance such as flushing, sweating, pallor, or weakness. Such cases are often thought to be due to attacks of hypoglycemia. Visceral seizures often spread to become generalized, and so visceral attacks are sometimes regarded as the aura of a generalized seizure.

A 45-year-old white male laborer had attacks which began with abdominal discomfort and profuse sweating. Frequently there had been an associated sensation of a lump in the throat and a feeling of suffocation. The symptoms would disappear spontaneously or would go on to become generalized, with loss of consciousness. With moderate doses of diphenylhydantoin (Dilantin; Parke, Davis) sodium U. S. P. and phenobarbital, the patient had considerable relief of his symptoms, although the attacks were not completely abolished.

A final word should be said about "subconvulsive seizures." Although a great deal has been written about the "epileptic personality" in the past, very little has been said concerning the theoretical effects of continued cortical seizure activity as seen in the electroencephalogram. We have repeatedly seen seizure patients with grossly dysrhythmic electroencephalograms, who clinically are extremely anxious, uneasy, inattentive, or hyperactive. Frequently, the history of this state goes back only as far as the beginning of the epileptic attacks. When seizures are controlled the symptoms often subside, and the patient or family notes this change. We cannot attribute this to the sedative effect of phenobarbital alone, because the improvement is usually not observed until the time that the patient becomes resistant to the sedative effects of the drug. Although this may be

a psychologic response to relief of seizures, we feel that it is a direct drug effect which in some way alters the effect of interseizure cerebral dysrythmia. An excellent review of "the hyperkinetic syndrome" and its relationship to epilepsy has been written by Ounsted.[9]

DIAGNOSIS

No distinction should be made among the terms seizure, convulsion, fit, epileptiform attack, spell, blackout, or epilepsy in general medical thinking. Seizures may be recognized for what they are if the characteristics of the attack correspond to known functions of various areas of the brain. Many of these symptoms have already been described. The cardinal characteristics of epilepsy are sudden onset, similarity between one attack and another, brief duration, and rapid resolution. Frequently attacks are followed by generalized headache, a period of confusion, and an interval of inescapable sleep. There is often alteration in the state of awareness, varying from mild confusion to coma. Amnesia for all or part of the episode is the rule (when there is not complete loss of consciousness during the spell). A useful outline for obtaining this information is as follows:

1. Description
   (*a*) Aura
   (*b*) Manifestations of seizure
   (*c*) Postseizure state
2. Duration of each component of above
3. Frequency of spells
   (*a*) Date of onset
   (*b*) Seizure cycle, frequency
   (*c*) Precipitating or ameliorating influences
   (*d*) Effect of medication
4. Childhood and family history
5. Functional capacity in seizure-free period

Careful analysis of each component of the seizure may enable the physician to describe the cerebral origin of the disorder. This is the initial part of the diagnosis. The second consideration is directed toward etiology. A seizure may be triggered off by such mild metabolic abnormality as a childhood fever or, on the other hand, it may be the first indication of an infiltrating glioblastoma. Many attacks occur without recognizable provocation. Others are preceded by brain trauma, infection, vascular disorders, metabolic diseases, toxic conditions, or emotional upset. A number of these factors may be present. Through the use of the electroencephalogram it is found that cerebral dysrhythmia is the common mechanism through which the seizure takes place. In many instances of "idiopathic epilepsy" the dysrhythmia is diffuse. Focal seizures are often accompanied by a localized EEG abnormality. Careful history-taking is the most important step in case evaluation. Seizures following brain injury of any type begin between the 3rd and the 12th month after the injury. This knowledge is of some help in the evaluation of attacks after strokes, infection, or trauma. The onset of focal seizures in adult life is commonly the sequella of arteriosclerotic or hypertensive vascular disease. In these cases strokes may be a part of the clinical picture. Brain tumors are suspected when the history is characterized by progressive disability between attacks. Sometimes headache or other evidences of increased intracranial pressure are present.

The electroencephalogram has contributed a great deal to the understanding of seizure mechanisms. An abnormal tracing is found in about 85% of seizure patients as compared with 10% in the average population. Thus it is seen that diagnosis must hinge on clinical impressions rather than on this test. However, the tracings may help in uncovering underlying diseases, aid in classification, and suggest possible therapy. The entire clinical picture must be taken into account in the interpretation of the record. Serial electroencephalograms are important in diagnosis, because the changing character of the EEG may suggest a gross brain lesion. Records taken at monthly intervals in tumor-suspect cases will often show evidence of a progressive lesion before marked clinical changes occur. Other definitive diagnostic procedures, for example, pneumoencephalography, arteriography, and ventriculography, should be carried out only after consultation with a neurologist or a neurosurgeon.

When the clinical examination and the EEG do not suggest an underlying disease, patients may be started on appropriate therapy without further diagnostic procedure. If the response is unsatisfactory or new symptoms appear, skull x-rays and spinal fluid examinations are indicated.

THERAPY

I. Grand Mal and Partial Seizures

The goal of therapy for patients with seizures should be complete control or total abolition of spells. In our experience this can be obtained in 80% of patients with grand mal epilepsy and in about 50% to 60% with partial seizures. The drugs of choice for both these types of seizures are diphenylhydantoin and phenobarbital, used in combination. Severe toxic reactions to these drugs rarely preclude their use, and they have withstood the test of time in alleviation of symptoms. A complete review of all drugs currently used in the treatment of epilepsy has recently been written by Drake.[10] It is the purpose of this paper to outline in detail the application of some of these agents. Improper manipulation of dosage has led to treatment failures. Treatment of each patient represents an experiment in itself. There are no standards of fixed dosage levels, nor can the amount used be regulated on the basis of total body surface or weight. Once the decision is made to use an anticonvulsant, the drug administration should be carried out systematically until seizures are controlled or toxic levels are reached. Agents other than diphenylhydantoin and phenobarbital should not be prescribed unless these two drugs are proved ineffective in this way.

A. Criteria for Treatment.—1. Absolute Indications: (*a*) Recurrent seizures, whether they are of unknown causes or are the result of brain trauma, infection, neoplasm, or vascular or metabolic disease.

(*b*) Within days or weeks of a single seizure if it has been a prolonged episode of convulsive activity (one to two hours) or if the seizure is confined to one extremity or one side of the body and is followed by (abnormal) symptoms or signs relative to the part involved in the seizure. An example of this would be a focal motor seizure with postseizure hemiparesis.

(*c*) If the seizure occurs within one year following brain trauma, infection, or vascular injuries.

(*d*) After a single grand mal seizure if the electroencephalogram is abnormal.

2. Questionable Indications: (*a*) A single seizure of less than 15 minutes' duration not accompanied by postseizure signs or symptoms which has occurred during a reversible metabolic abnormality. An example of this would be a single childhood febrile convulsion or withdrawal from prolonged barbiturate or alcoholic addiction.

B. Rationale of Treatment.—Although epilepsy is a paroxysmal disorder, as a general rule the chance of future seizures increases with each convulsion. Brain damage is observed to occur after repeated seizures or following single seizures, particularly in infants and elderly patients. In addition to the disability that may result from the loss of mental, motor, or sensory functions, there is electroencephalographic evidence that new seizure foci develop in areas of injured cortex. Thus a vicious series of events, namely, the seizure, brain injury, development of the seizure focus, and more seizures, is set up.

C. Specific Measures.—1. The Seizure: The frightening specter of a patient convulsing, apneic, cyanotic, bleeding, and frothing at the mouth elicits an all-out instinct to be helpful. No drugs need be administered, since a single seizure is self-limited. The patient should be protected from harm by removing objects nearby which might injure him. Once the teeth are clenched it is not practical to try to prevent tongue biting. The patient's pharynx can be cleared of pooled secretions once the tonic phase has ended. Postural drainage with the head turned to one side is very effective. Mechanical aspiration should be used if it is available. Respirations begin spontaneously when the seizure ends. Administration of respiratory

stimulants, for example nikethamide (Coramine), is dangerous and should not be employed. The patient should be touched as little as possible during a convulsion, or psychomotor seizure, since the attacks are frequently prolonged by physical contact or restraint.

Prolonged attacks should be terminated by a single deep-sleep-producing dose of intravenous amobarbital (Amytal) sodium to prevent status epilepticus.

2. Status Epilepticus: Continued seizures without conscious intervals between convulsions may lead to death unless terminated by adequate treatment. The patient must be heavily sedated and kept in deep sedation for 24 hours. This is best accomplished with a solution of amobarbital sodium U. S. P., 1.0 gm. in 20 cc. of water for injection U. S. P. given slowly intravenously at the rate of 1 or 2 cc. per minute until the seizure stops and deep sleep results. Sleep is maintained with a continuous intravenous drip of 0.5 gm. amobarbital sodium in 500 cc. of isotonic saline solution. The patient must be turned every one-half hour to prevent hypostatic and aspiration pneumonia. Mild Trendelenburg position is maintained, and mechanical aspiration of secretions is often necessary. Oxygen is given through a nasal catheter when indicated.

Additional sedation may be obtained without depressing respiration with the use of paraldehyde suppositories each containing 4.5 cc. paraldehyde, repeated every four hours. Diphenylhydantoin sodium in oil capsules is available for rectal administration, each capsule containing 0.1 gm.; 0.2 gm. is administered three times daily after a cleansing enema.

Inadequate sedation can be more harmful than no sedation at all. It has been shown electroencephalographically that seizure activity is most prominent during the state of light sleep,[11] and it has been noted clinically that patients may have seizures only during their periods of twilight sleep. Therefore, if the patient is kept in a drowsy state he is likely to convulse. It is wiser to allow the patient to awaken fully rather than to maintain a state of partial sedation.

3. Interseizure Management: The burden to the patient of bearing the label epileptic may be lightened if there is understanding of the nature of the disorder. It is a common notion that the future will bring mental deterioration, insanity, or uncontrollable impulsive and destructive behavior. This attitude must be replaced by more realistic thinking. Properly controlled epileptics may lead a normal life. Restriction of physical activity, regulation of diet, and limitation of social aspirations are unnecessary. The family circle will need help in accepting the patient as they would if seizures had never occurred. Confidence in the physician and his ability to prevent seizures helps greatly in this understanding.

Medication must be taken at a constant daily rate. The usual starting dose of diphenylhydantoin sodium for adults is 0.1 gm., taken three times daily after meals, to avoid gastric irritation. This is used in combination with phenobarbital, 0.1 gm. at bedtime. Except for young children, we see no advantage in using divided doses of phenobarbital routinely, since the anticonvulsant effect of single-dose administration lasts over 24 hours, while any hypnotic effect is utilized during the sleeping hours. Children are begun on smaller doses; up to the age of 6 months, diphenylhydantoin sodium 30 mg. per day and phenobarbital 15 mg. twice daily; 6 months to 2 years, diphenylhydantoin sodium 60 mg. daily and phenobarbital 30 mg. twice daily; between the ages of 2 and 6 years, diphenylhydantoin sodium 0.1 gm. and phenobarbital 30 mg. twice daily; from 6 to 12 years, diphenylhydantoin sodium 0.1 gm. twice daily and 0.1 gm. of phenobarbital at bedtime. After the age of 12 adult dosages are used. These two agents are used together in gradually increasing doses. First one is explored to the point of toxicity, usually diphenylhydantoin first, and then reduced and maintained at just below toxic levels. Then the other is gradually increased in the same

way. If seizure control is not obtained before toxic levels are reached with these drugs, other agents are added.

4. Changing Medication: Full diphenylhydantoin effect ("dilantinization") occurs after five to seven days of continuous treatment. This is to be taken into consideration when seizures occur during the first week of treatment, since the usual seizure pattern will not be interrupted during that interval. Each increase in diphenylhydantoin may be followed by a similar period in which there is no added protection. Diphenylhydantoin sodium is increased in increments of 0.1 gm. daily. When seizures regularly occur at a specific time of day, it is often beneficial to add an extra capsule one to two hours before the usual time of the seizure. If seizures occur at random intervals, the time the extra medication is taken is not so important. When seizures occur at weekly or more frequent intervals, the optimum dose can be reached quickly by graded increases at two-week intervals. If the usual pattern of attack is infrequent, it may take months to attain full control with this method. Therefore, when only two or three convulsions a year occur, diphenylhydantoin may be given four or five times daily at the beginning of treatment and continued at this level if toxic symptoms do not occur.

(*a*) Diphenylhydantoin intoxication. Symptoms that require reduction of daily dosage include unsteady gait, thick speech, blurred vision, and a mental picture not unlike that of mild alcoholic intoxication. The physical signs may include all or some of the following: dilated pupils, nystagmus, ataxia of the trunk, and incoordination in movements of the extremities. Seizures may increase in frequency during periods of diphenylhydantoin toxicity.

The drug should be stopped entirely until the nystagmus and ataxia disappear. This is usually only one or two days. It is then restarted at a lower level. The patient may be uncontrolled taking 0.3 gm. of diphenylhydantoin sodium daily and may be intoxicated at 0.4 gm. per day, but on 0.3 gm. one day and 0.4 gm. the next he may do very well. It is often not recognized that such slight changes can make such great differences. Adults may tolerate 0.5 to 0.6 gm. daily without toxic symptoms.

(*b*) Toxicity due to diphenylhydantoin sensitivity. Bone marrow depression resulting in agranulocytosis is so uncommon that routine periodic blood cell counts are unnecessary. That diphenylhydantoin is capable of producing megaloblastic anemia appears to be fairly well documented,[12] but this is certainly a rare occurrence.

Morbilliform rash is infrequent. It appears during the first two weeks of medication, usually on about the 10th day, often disappears spontaneously even if the drug is continued, and may not recur if the drug is stopped and then again restarted.

Hypertrophy of gums is more frequent in children than in adults. It accompanies poor oral hygiene. Excess tissue can be surgically removed and recurrence prevented by daily gum massage. Diphenylhydantoin need not be discontinued. Gastrointestinal discomfort occasionally results from the alkalinity of the drug. Taking the medication with food or after meals alleviates this distress in most instances. For those still troubled, capsules of diphenylhydantoin sodium in oil are available.

(*c*) Phenobarbital toxicity. Sleepiness is a limiting factor, but it is worth while allowing for a suitable period to elapse in the hope that tolerance to sedation will develop. Children may become hyperactive and irritable on small doses of phenobarbital but do very well on larger amounts. Bone marrow depression and skin eruptions are infrequent complications in the use of this drug. The effect is reversed when the agent is withdrawn, and it can be used again without toxic manifestations.

5. Other Therapy: Methylphenylethyl hydantoin (Mesantoin) is a valuable anticonvulsant not routinely used because it is a bone marrow depressant. Patients uncontrolled on usual medication are maintained on diphenylhydantoin and phenobarbital and

maximum amounts of methylphenylethyl hydantoin are added in increments of 0.1 gm. a day at intervals of two weeks, or less frequently, until seizures are controlled or a daily intake of 0.5 gm. is reached. If this proves ineffective, other agents, such as N-benzyl-β-chlorpropionamide (Hibicon), primidone (Mysoline), or newer agents are tried in similar fashion. The toxicity of phenacemide (Phenurone) limits its use to exceptional cases. There is not yet conclusive proof that sodium diuresis adds to the efficacy of anticonvulsive medications. Acetazoleamide (Diamox) is an agent currently undergoing study from this standpoint. For details in the use of these other agents, the reader should refer to the comprehensive review of Drake.[10]

The surgical treatment of epilepsy may become a useful adjunct to drug therapy but has not yet come into general use. Surgical procedures have been reserved for drug-resistant patients, who make up a minority of the epileptic population.[13]

6. Termination of Drug Therapy: Abrupt withdrawal of anticonvulsant agents may precipitate seizures or even status epilepticus within 24 to 48 hours. Therefore intermittent therapy should never be undertaken with any of the drugs discussed. When a patient is taken off medication it is reduced at monthly intervals in increments similar to those used in building up the dosage but never discontinued all at once. This applies to changes of medications as well as to permanent discontinuance of anticonvulsant therapy.

After a patient has been seizure-free for five years, consideration is given to withdrawing medications. Marked electroencephalographic abnormality indicates a need for continued therapy, while a normal electroencephalographic pattern suggests that medication may be slowly reduced and finally eliminated. However, even in the presence of a normal EEG, seizures may recur, at which time anticonvulsants should be restarted at levels that originally brought the seizures under control and the drugs must be maintained at that level. There is no evidence of chronic toxic effect or addiction after prolonged use of these agents.

II. Petit Mal

Trimethadione U. S. P. (Tridione) or paramethadione (Paradione) are the drugs of choice in the treatment of petit mal and have some use in other seizures accompanied by spike-wave EEG patterns. In contrast to other agents discussed, these have a rapid action and may be stopped abruptly without danger of precipitating seizures. The usual dose for children and adults is 0.3 gm. three times daily. Increases may be made weekly, but little is to be gained in dosage higher than 0.3 gm. taken six times a day. Toxic symptoms include photophobia, scarlatiniform rash, and bone marrow depression. Periodic blood cell counts should be done. The photophobia may be transient. A rash may precede leucopenia. Either of these two complications call for drug withdrawal until symptoms clear. In some cases it is possible to restart medication without ill effects. Some children may have grand mal as well as petit mal attacks. The general practice is to control the grand mal with diphenylhydantoin and phenobarbital before instituting trimethadione or paramethadione. This is done because there is some feeling that trimethadione may increase grand mal, but perhaps more important is the fact that petit mal does not usually cause brain damage, and thus it is more important to the patient to have the major attacks controlled.

PROGNOSIS

Probably no other major chronic disease has such a favorable prognosis as epilepsy, provided adequate therapy is carried out. In contrast to the dismal outlook that confronted him only a few decades ago, the epileptic may now look forward to a useful life with control of his disease. In some cases, after prolonged antiepileptic therapy, a remission may be obtained so that drugs are no longer needed. So long as the seizures are controlled the epileptic no longer needs to fear

progressive mental deterioration. The reclusive life sought by so many of the afflicted in the past has been abandoned in favor of more social and productive careers.

REFERENCES

1. Lennox, W. G.: President's Address, A. Res. Nerv. Ment. Dis., Proc. **26**:xv-xix, 1947.

2. Gastaut, H.: The Epilepsies: Electro-Clinical Correlations, Springfield, Ill., Charles C Thomas, Publisher, 1954.

3. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man: A Clinical Study of Localization of Function, New York, The Macmillan Company, 1950.

4. Williams, D.: Cerebral Basis of Temperament and Personality, Lancet **2**:1-4, 1954.

5. Gastaut, H.: Interpretation of the Symptoms of Psychomotor Epilepsy to Physiologic Data in Rhinencephalic Function, Epilepsia **3**:84-88, 1954.

6. Gloor, P.: Electrophysiological Studies on the Connections of the Amygdaloid Nucleus in the Cat: I. The Neuronal Organization of the Amygdaloid Projection System; II. The Electrophysiological Properties of the Amygdaloid Projection System, Electroencephalog. & Clin. Neurophysiol. **7**:223-264, 1955.

7. Mulder, D. W.; Daly, D., and Bailey, A.A.: Visceral Epilepsy, A. M. A. Arch. Int. Med. **93**: 481-493, 1954.

8. Phizackerley, P. J. R.; Poole, E. W., and Whitty, C. W. M.: Sino-Auricular Heart Block as an Epileptic Manifestation, Epilepsia **3**:89-91, 1954.

9. Ounsted, C.: The Hyperkinetic Syndrome in Epileptic Children, Lancet **2**:303-311, 1955.

10. Drake, F. R.: The Current Drug Therapy of Epilepsy: A Review, Am. J. M. Sc. **230**:98-107, 1955.

11. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography: Vol. 2. Epilepsy, Ed. 2, Cambridge, Mass., Addison-Wesley Press, 1952, p. 19.

12. Ryan, G. N. S., and Forshaw, J. W. B.: Megaloblastic Anemia Due to Phenytoin Sodium, Brit. M. J. **2**:242-243, 1955.

13. Meyers, P.: The Surgical Treatment of "Focal" Epilepsy: An Inquiry into Current Premises, Their Implementation and the Criteria Employed in Reporting Results, Epilepsia **3**:9-36, 1954.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY, 1955

STANLEY COBB, M.D., Cambridge, Mass.

DURING the last two years there has been a great increase of interest in the use of drugs in psychiatry. Of course there is nothing new in the idea that drugs might alleviate mental ills. Caffeine has been used for centuries to produce euphoria, to increase flagging energies, to make a dull life bearable, and to make a strenuous life possible. The per capita consumption of coffee in the United States has risen from 6.5 lb. in 1853 to 16.9 lb. in 1953. One has only to observe how quickly radio commentators and the Congress react to a rise in the price of coffee to realize the widespread importance of neuropharmacology. Alcohol has another long and complex pharmacological and social history. Morphine formerly was extensively used in psychiatry. Later bromides took over. The first half of the 20th century has seen the rise (and perhaps the beginning of the fall) of the barbiturates.

Endocrine therapy was once a source of great hope in psychiatry, followed by general disappointment. Thyroid is beneficial in a few cases. Adrenergic drugs like amphetamine are useful as stimulants. Recently the fact that cortisone and corticotropin (ACTH) have caused many schizoaffective reactions has aroused much speculation as to the role of the hormones in schizophrenia. Quarton [1] has discussed the various theories of the action of hormones on the brain and has shown that much more investigation must be done before we understand these induced psychoses. But the fact that they can be induced is a hopeful lead. An important contribution is the observation of Bower and Altschule [2] that practically all patients with postpartum psychoses respond remarkably well to progesterone, whereas formerly almost half of them went on to chronic schizophrenia.

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PHARMACOLOGY OF THE BRAIN

In a quite different group of drugs, the ergot derivatives, psychotic effects have also been found. Hoffmann [3] in 1943 discovered that *d*-lysergic acid diethylamide (LSD) caused not only autonomic changes but also visual hallucinations, dreamy states, and restlessness. In the last five years much work has been done on the experimental psychoses brought on in human volunteer subjects by LSD.[4] A reaction that resembles a severe psychosis can be induced and lived through its various stages in from 6 to 12 hours. Not only is this important for the understanding of the disease process and its treatment but it can give to a psychiatrist who is willing to undergo the experiment an intimate understanding of what his patients are experiencing.

An internationally known politician has urged that a new department of science, to be known as "chemical psychology,"[5] be studied in the hope that specific relationships could be found between certain chemicals and human behavior. He thought of discovering chemicals that might cause whole populations to become passive and eschew war. He mentioned the possibility "of inventing cocktails to clear thoughts and to enable representatives to work day and night in urgent situations." He mentioned some dangers.

BRAINWASHING

"Brainwashing" is the unfortunate term that has been played up recently to give the negative side of this picture. Much of the debasing influence exerted on prisoners has been, of course, psychological, by wearing them down with repetitive stimuli, boredom, hunger, fatigue, and pain and by tempt-

ing them with subtly increasing rewards.[6] But there is evidence that drugs also have been used on prisoners to break down morale, change points of view, and obtain "confessions."[7]

Santucci and Winokur[8] believe that the essential elements of "brainwashing" are psychological. They describe a patient who spent 33 months in a Korean prison camp and became mentally deranged only on return to the United States, as follows:

> The patient in the course of brainwashing was forced into singing Communist songs and writing pro-Communist statements. Although at first he probably did not accept these, he was rewarded for his activities, and consequently the behavior must be considered as having been reinforced. The role of a high-drive state as a result of hunger and the assuagement of the hunger as a reward must be taken into account. Further, he was given tasks to accomplish by his captors and received various types of gratification for these activities. If, in the beginning, the patient did not believe in his statements and activities, there would have inevitably been an internal conflict between his motor and speech responses as opposed to his thinking. Only three ways were available in which to resolve this conflict. The patient might have been able to outwit his captors, as some of the interviewees were able to do, or he could have refused to do their bidding, which would have resulted in punishment and no rewards. Either of these two ways of handling the situation would have resulted in a resolution of the conflict. Either of these methods would have provided a short-lived conflict with authority, which would, judging from the interviews of the POW's who successfully handled the brainwashing, have abated in time. Or the patient could have started to resolve the conflict by thinking in favor of his captors, and from the clinical material, this is what he finally did. The proof of this was his being sent to a camp for more intensive indoctrination, a thing which probably would not have happened had he not been viewed by the captors as brainwashed, at least in part.

They bring up the theory that much of the procedure used by the "Communists" is based on the conditioned reflex techniques of Pavlov, using rewards, reinforcement, and repetition to accomplish a learning process against the will of the subject. Meerloo,[9] in Montreal, believes that "Pavlovian strategy" is an important part of the technique that breaks down the prisoners' thinking processes. The difficult differentiations that the prisoner has continually to make between what is proper to do and what improper according to his code may well be a factor in causing anxiety symptoms. Pavlov's dogs were made "neurotic" by being forced to make more and more difficult discriminations between stimuli, for example, the difference between an ellipse and a circle or between two notes on a tuning fork.

Some investigators believe that chemical substances have been found that have specific psychological influence on human subjects. Except in a limited way, no chemical can have a "specific," constant and repeatable effect on the behavior of an organism as complex as man. Therapy applied to a man, be it surgical, electrical, or chemical, can only bring out in his behavior the pattern that is already there. This pattern is built up in the brain by life experience. It is the pattern that determines the man's "personality," "character," or "morality." And since the experience of every man differs from that of every other man, no two personalities or characters are alike. Therefore, the hope of finding a drug to cause a "specific" reaction on any number of men becomes an illusion.

When I say that in a limited way chemicals may have specific effects on humans, I refer to such gross changes in clinical behavior as depression, elation, hallucination, delusion, sleep, stupor, coma, and death. The content of thought in these varied clinical states will be different for each person. It will be determined by his past experience. In a recent study of drug effects on man Lasagna and his colleagues[10] say, "In addition to the dose and route of administration, the nature of the subject and the situation in which the drug is administered are important determinants of drug effects." The moral of all this would seem to be that training in "good morale" is the only way to combat "brainwashing." (What is considered "good" of course varies from one social unit to another.) Men of the highest morale, however, can be broken down by prolonged exhaustion, pain, hunger, and occasionally the administration of drugs.

NEUROPHARMACOLOGY

The painstaking and carefully controlled work of experts in neuropharmacology is exemplified by the fundamental research reported in the transactions of the first conference on that subject held under the auspices of the Macy Foundation.[5] There is an excellent chapter by Kety on the effects of pharmacological agents on the circulation and metabolism of the brain in man. In the next chapter Scharrer describes a technique for the study of circulation of the blood in focal areas of the brain in animals. The method shows much promise. In Chapter 3 Brazier describes her work on the effect of thiopental (Pentothal) on auditory and visual stimuli as they are electrically recorded in the human brain. Here is given a very specialized electrical technique for the recording of the effects of an anesthetic. Many problems fundamental to neurophysiology and anesthesia are discussed by an unusually competent group. Magoun gives, in Chapter 4, the relation of anesthesia and levels of awareness to the ascending reticular system of the brain-stem in monkeys. In the last chapter Pfeiffer reports some remarkable experiments showing changes within the nerve cell following the administration of convulsants to rats.

This book gives an idea of the research going on in that area of pharmacology that applies to neurology and psychiatry. There is much keen discussion reported, and many references are given to similar careful investigations by others. This sort of research is in marked contrast to the flood of "literature" that has inundated the practicing physician in the last two years concerning the new "tranquilizing" drugs. Even if these drugs really do make tense and hurried persons "relax" and become "tranquil," one wonders about the wisdom (and the morality) of giving drugs to accomplish a result probably better achieved by improving the person's social adjustment. What would the United States be like if we relaxed the hurry, scurry, rush and tranquilized the "go-getters"? Why not just drop that 17 lb. of coffee?

TRANQUILIZING DRUGS

It is remarkable that several new sedative and relaxant drugs, quite different from each other in source and chemistry, should have been developed in the last three years. I shall discuss three of these—meprobamate (Miltown, a propane dicarbonate) *; reserpine, an alkaloid of the ancient Indian drug Rauwolfia,[13] and chlorpromazine,† a synthetic derivative of phenothiazine. Meprobamate has been used on a smaller number of patients and has not been as widely advertised as the other two, but the data so far available indicate that it may be a useful drug. It apparently works as an interneuronal blocking agent that relaxes muscles and reduces reflexes. Chlorpromazine (Thorazine; Largactil; Megaphene) and reserpine (Serpasil) are of equally recent origin, but they have been widely advertised and already tried out on thousands of patients. Because the "literature" on these two has been so enormous, reference is only made to a few of the summarizing papers. Special conferences and symposia have been held on each of these two drugs.

From the chemical standpoint they have some significant relationship. Chlorpromazine is closely related to several drugs that cause hallucinations (adrenochrome, harmine, and bufotenin) and to some drugs which relieve the symptoms of paralysis agitans. This is especially intriguing when one learns that large doses of chlorpromazine may cause "Parkinsonism," the syndrome of paralysis agitans. Reserpine, a quite different drug, frequently causes temporary "Parkinsonism" in patients. Chlorpromazine has been synthesized by special chemical techniques and was chosen for clinical use after much physiological experiment. Reserpine is an alkaloid first crystallized out of the crude Rauwolfia serpentina in 1952. Rauwolfia is an herb which has been used for hundreds of years in India as "the insanity herb."

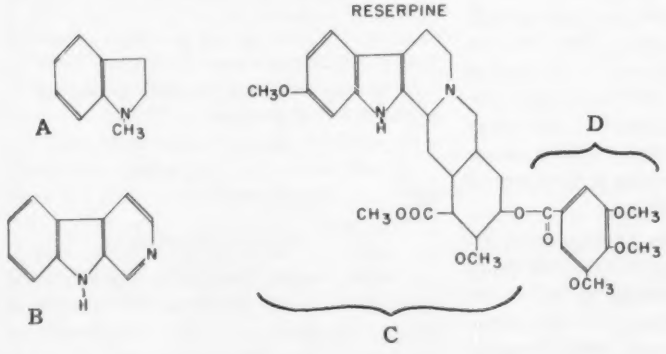
Reserpine has a remarkable chemical formula (Fig.). Its basis is much like the formulas of adrenochrome and harmine, both

* References 11 and 12.
† References 14 and 15.

of which are drugs which cause hallucinations when administered to normal persons. When two more rings, a $COOCH_3$ group, and a OCH_3 group are added to the harmine formula, one has a formula resembling that of yohimbine, a strong and toxic sympathicolytic drug. When, finally, a mescaline-like radical is added to this, the total formula is that of reserpine. Mescaline is a drug well known as a producer of delusions and hallucinations. It will take much careful work to elucidate these intricate pharmacological relationships, but the importance for psychiatry of such research is obvious.

The question as to whether or not chlorpromazine and reserpine actually reproduce the syndrome of paralysis agitans is important. Clinical descriptions of the symptoms frequently seen after reserpine therapy, less frequently after chlorpromazine, certainly suggest that a state something like "Parkinsonism" is produced. As far as I know, however, patients showing this syndrome have not been carefully tested by laboratory methods to see if the syndrome is a true reproduction of the Parkinsonian state, with its characteristic motor phenomena. This should be carefully done, because it would surely be of great interest from the pharmacological standpoint if two drugs as different as chlorpromazine and reserpine could produce "Parkinsonism." It would also be important because two drugs very similar to chlorpromazine in chemical formula, 10-(2-diethylaminoethyl) phenothiazine (Diparcol) and 10-(2-diethylamino-1-propyl) phenothiazine (Parsidol), relieve the symptoms of paralysis agitans, especially the tremor.

From physiological experiments it is found that both drugs depress hypothalamic reflexes; both cause hypotension and depress vomiting reactions and sham-rage in animals. Chlorpromazine is rapid in its hypotensive effects; reserpine is slow. Reserpine has only slight antivomiting action, while in chlorpromazine the effect is conspicuous. Chlorpromazine depresses the activating action of the reticular formation of the midbrain, whereas reserpine is said to enhance it. Conditioned reflexes are found to be depressed by chlorpromazine but are not affected by reserpine. Paradoxically, it is found that the avoidance reactions to frightening stimuli are greatly depressed by reserpine but only slighty depressed by chlorpromazine. Gastric secretion is increased by reserpine and decreased by chlorpromazine. A great deal of physiological work is being done on these two drugs. The statements made above need corroboration, but the investigations will surely be fruitful both in teaching us the pharmacology of the drugs and in elucidating important points in neurophysiology.



A, adrenochrome ring system; *B*, harmine ring system; *C*, yohimbine-like portion of reserpine; *D*, mescaline-like portion of reserpine.

Much is known about the clinical effects of these drugs because of extensive and, at times, too intensive use. The paper by Bleuler and Stoll,[14] comparing the therapeutic use of reserpine and chlorpromazine at the Bergholzli hospital in Switzerland, is one of the best balanced reviews I have seen. They emphasize that either drug may be a complete failure in an individual patient but that

the other, or both together, may be effective. They also state that chlorpromazine may be harmful by forming a habit in some patients. It has more tendency to cause euphoria, and it works more quickly. Reserpine acts more slowly and has longer-lasting effects, but it occasionally causes periods of excitement both early in treatment and secondarily, after treatment has been under way two or three weeks.

There is no doubt that both drugs are highly effective in reducing restlessness, agitation, and aggressiveness in patients, whether these behavioral phenomena are due to mania, schizophrenia, senile dementia, delirium, or drug withdrawal. Thus the patient can soon be placed in a better environment and he can make much better contact with his physicians and has more opportunity to benefit from psychotherapy. One sees also what a boon such improvement in behavior is to the nursing staff and the hospital administration. In fact, the number of leucotomy operations and the amount of electroshock therapy is rapidly diminishing in most mental hospitals that use these drugs.

It is obvious from the many clinical reports, however, that enthusiasm for the drugs is most marked in large hospitals where the staff is small and the load of patients is great. In smaller psychiatric units with plenty of nurses and psychiatrists the evaluation of the drugs is much more guarded. This may mean that close individual psychiatric supervision and nursing are still the best methods of treatment. The remarkable improvement reported in many chronic patients may be partly due to increased attention by the staff and an atmosphere of therapeutic optimism. More closely controlled studies are needed to evaluate these factors.

The harmful side-effects are rare and are usually reversible when the drug is discontinued. Jaundice is caused by chlorpromazine in about 1% of cases and is probably due to an allergic reaction. The jaundice is due to obstruction within the small bile passages. The function of the liver cells is not impaired. Reserpine causes nausea and diarrhea not infrequently; gastric ulcer and even perforation occur rarely. Both drugs can cause the patient to develop the syndrome of paralysis agitans: in treatment with reserpine this is common; with chlorpromazine it is rare unless large doses are given rapidly. In both cases the syndrome appears to be temporary. A few cases of agranulocytosis have been reported after chlorpromazine. Both drugs commonly cause weakness, dizziness, fainting, and feelings of great fatigue. These symptoms are obviously related to their hypotensive action and should be treated by bedrest and adequate nursing care. Accidents have happened when the drugs were given to ambulatory patients.

In summary I cannot do better than quote Altschule [15]:

> Chlorpromazine and reserpine have changed psychiatric treatment greatly in the last two or three years; as far as can be judged at present their chief value in therapy is that they
>
> (a) produce conditions favorable to recovery in acute, self-limited psychoses;
>
> (b) ameliorate anxiety in many syndromes
>
> (c) make behavior, if not thinking, more nearly normal in chronic psychoses.

HUMAN GENETICS

Several books have been published on heredity that are of practical interest to physicians. Sheldon Reed,[16] the director of the Dwight Institute of Human Genetics at the University of Minnesota, has condensed into a small book most of the useful knowledge that a physician needs when consulted by a family about problems of heredity. It is well written and well arranged. He sums up the much-discussed problem of schizophrenia by expressing the opinion that schizophrenia has a genetic basis and that the expression of the heredity is subject to the total environment encountered. He adds a hopeful note at the end, saying, "A careful study of the physiologic differences between the discordant twins may provide the clues needed for a medical cure and prevention of the disease." He considers the evidence for heredity as a cause of manic-depressive psychosis as even more convincing. Neel and Schull,[17] of the University of Michigan, have written a fine book on the principles of human

genetics that will give the more advanced student a sound knowledge of the subject.

From Utrecht comes a thorough monograph by DeJong [18] on the myotonic dystrophies. This supplements the classical contributions of Thomasen, from Copenhagen, seven years ago and brings the subject up to date. DeJong is inclined to emphasize small variations in the clinical picture and describes many syndromes. He decries the unitarians who emphasize the genetic relationships and consider the larger groups of syndromes as the significant entities.

The Association for Research in Nervous and Mental Disease has published a volume on "Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns." [19] This is the report of their annual meeting, at which a distinguished group of geneticists and clinicians presented papers. The first six chapters are on the less specialized aspects of human heredity. There is an excellent introductory paper by David and Snyder on "Principles of Human Genetics." This will bring up-to-date the physician who has not recently read much about genetic theory. A paper by Davis on "Genetics and Environmental Control of Enzyme Formation and Activity" gives a look into the future; it is a most interesting explanation of the possible enzymatic mechanisms taking place in the genes. A chapter by Warkany and Wilson on the prenatal effects of nutrition deals with cerebral changes due to deficiency of copper and of thyroid. The effects on the young are often called "constitutional" but are not hereditary (except in rare cases where cretinism is hereditary). They are the effects of environmental changes upon the embryo. In Chapter 5 Anastasi discusses the inherited and acquired components of behavior. This is an important contribution, because it brings out the fact that there is much uncritical thinking about the so-called heredity-environment problem. The author points out that the more precisely heredity and environment are defined and the more fully their operation is investigated the more evident it becomes that they are inextricably intertwined. The distinction between them no longer appears as sharp as it once did; heredity and environment are themselves abstractions; each covers a multiplicity of factors which interact with each other. In discussion Scott pointed out that interaction is not a good concept because it means that two or more factors modify each other, and this does not exactly describe the situation in regard to heredity and environment, because in any given individual the genes themselves are well protected from environmental effect. Both the genes and the environment modify the developing organism, and their action may be to work together (co-action) or they may work in opposite directions (counteraction). In the same discussion Beach points out that whether a trait is directly and profoundly influenced by genic factors or is shaped principally by nongenic forces is of little or no importance unless one is interested in two or more generations of individuals. He emphasized that genetically controlled characters are not necessarily unmodifiable in the individual and that environmentally determined traits are, on the other hand, often exceedingly resistant to change. The attempt to demonstrate the hereditary nature of a given pattern of behavior by ruling out the possibility of modification through experience is often very difficult. One problem lies in our limited understanding of just what learning is and how it can be recognized and controlled. Still another source of difficulty in separating the "inherited" from the "learned" components of behavior stems from earlier failures to recognize the contributions of early experience which do not fit into the category of learning as currently conceived.

Many psychologists and zoologists [20] believe that the concept that "instinctive acts" are innate, hereditary forms of behavior is no longer tenable. They believe that the ethologist's [21] description of neuronal patterns, inhibitory mechanisms, and releasers is too schematic. They point out that modern students of embryological development show that from the very beginning the development of the embryo is greatly influenced by environment. The genes in the chromosomes

in each cell are primary guides as to how the cells shall grow and form tissues. But they can guide only in relation to the continuous environmental forces. The first of these is the sum of the chemical changes in the fluid environment as cells multiply and differentiate. At first the changes are simple, for example, the effects of oxygen, carbon dioxide, and electrolytes, but later there are complex effects such as those from hormones.

The second, and equally important force, is the impact of the nerve impulses. They come from sense organs and play on the growing nervous tissue as physicochemical stimuli. Their presence or absence affects maturation of the nervous tissue. They guide its growth by a feed-back process; they cause it to function with its efferent parts, and this leads to more afferent stimuli. In its earliest and simplest form this is called "experience" of the nerve cells; later in the maturer nervous system it attains the dignity of "learning." Thus, the genic influences guiding the growth of the organism are basically important but certainly are not the only directing influences. In fact, Fuller [22] states that "development is a continuous transaction between the organism and its surroundings" and follows this with the definition that "heredity is the capacity to utilize an environment in a particular way." His little book is the best guide that I have seen to a modern concept of genetics in relation to human problems.

The study of the muscular atrophies and dystrophies is one of the most confusing subjects in neurology. McKay ‡ more broadly terms it the group of polymorphous neuroabiotrophies. In the chapter by Schut § some of the diseases in this broad field are discussed under the title of "Hereditary Ataxia." For example, in Friedreich's ataxia there are symptoms pointing to abnormality of many different systems of neurons. Schut gives a thorough review of the pathology and emphasizes the variability in symptoms and lesions. In discussion it was brought out that one can see in the familial neurological disorders a great number of items of clinical abnormality which are represented by variable constellations of symptoms making up the different clinical syndromes. There are many intermediate syndromes, with much overlapping. These conditions have been described under such varying titles and with such neurological meticulousness that only the specialist can be expected to keep the different syndromes clearly in mind. Too often even the neurologist merely describes a clinical picture and attaches to it a name, without seeing its biological relationship to other syndromes. Several authors have tried to describe "new diseases" without pathological data and without understanding that in hereditary diseases the genotype may be relatively constant, whereas the phenotype may vary greatly according to developmental and environmental influences. The point of view that this group of neuromyopathies should be looked on as one disease with many variants is at last being accepted. The commonest expressions of this genetic disease are seen in peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic neuritis (Dejerine-Sottas), spinal ataxia (Friedreich), cerebellar ataxia (Marie), and optic atrophy (Leber), but some 50 variants are described in neurological literature, many being called "separate diseases" and "specific entities," which they certainly are not.‖

‡ Reference 19, p. 318.

§ Reference 19, p. 293.

34 Fernald Dr. (38).

‖ Reference 19, p. 316.

REFERENCES

1. Quarton, G. C.; Clark, L. D.; Cobb, S., and Bauer, W.: Mental Disturbances Associated with A. C. T. H. and Cortisone, Medicine **34**:13, 1955.

2. Bower, W. H., and Altschule, M. D.: The Use of Progesterone in the Treatment of Post-Partum Psychosis, New England J. Med. **254**:157, 1956.

3. Stoll, A.; Hoffmann, A., and Troxler, F.: Über die Isomerie von Lysergsaure und Isolysurgsaure, Helvet. chim. acta **32**:506, 1949.

4. Rinkel, M.; Hyde, R. W.; Solomon, H. C., and Hoagland, H.: Experimental Psychiatry: II. Clinical and Physio-Chemical Observations in Experimental Psychosis, Am. J. Psychiat. **111**:881, 1955.

5. Abramson, H. A., Editor: Neuropharmacology, Transactions of the First Conference, New York, Josiah Macy, Jr. Foundation Publications, 1955.

6. Maloney, J. C., Psychic Self-Abandon and Extortion of Confessions, Internat. J. Psycho-Analysis **36**:53, 1955.

7. Swift, S. K.: The Cardinal's Story, New York, The Macmillan Company, 1950.

8. Santucci, P. S., and Winokur, G.: Brainwashing as a Factor in Psychiatric Illness, A. M. A. Arch. Neurol. & Psychiat. **74**:11, 1955.

9. Meerloo, J. A. M.: Pavlovian Strategy as a Weapon of Menticide, Am. J. Psychiat. **110**:809, 1954.

10. Lasagna, L.; von Felsinger, J. M., and Beecher, H. K.: Drug Induced Changes in Man, J. A. M. A. **157**:1006, 1955.

11. Selling, L. S.: Clinical Study of a New Tranquilizing Drug, J. A. M. A. **157**:1594, 1955.

12. Borrus, J. C.: Study of Effect of Miltown on Psychiatric States, J. A. M. A. **157**:1596, 1955.

13. Miner, R. W., Editor: Reserpine in the Treatment of Neuropsychiatric, Neurological and Related Clinical Problems, Ann. New York Acad. Sc. **61**:1-280, 1955.

14. Koetschet, P., and others: Symposium on Chlorpromazine in Clinical Medicine, Internat. Rec. Med. & Gen. Practice Clinics **168**:295, 1955.

15. Altschule, M.: The Use of Chlorpromazine and Reserpine in Mental Disorder, read before the American Association for the Advancement of Science, Gordon Conference on Medicinal Chemistry, Colby College, New London, N. H., Aug. 9, 1955; New England J. Med., to be published.

16. Reed, S. C.: Counseling in Human Genetics, Philadelphia, W. B. Saunders Company, 1955.

17. Neel, J. V., and Schull, W. J.: Human Heredity, Chicago, University of Chicago Press, 1954.

18. DeJong, J. G. Y.: Dystrophia Myotonica, Paramyotonia and Myotonia Congenita, New York, VanGorcum & Company, 1955.

19. Hooker, D., and Hare, C. C., Editors: Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns, A. Res. Nerv. & Ment. Dis., Proc. **33**:425, 1954.

20. Schaffner, B., Editor: Group Processes: Transactions of the First Conference, New York, Josiah Macy, Jr. Foundation Publications, 1955.

21. Thorpe, W. H.: Some Concepts of Ethology, Nature, London **174**:101, 1954.

22. Fuller, J. L.: Nature and Nurture: A Modern Synthesis, New York, Doubleday & Company, Inc., 1954.

Case Reports

POSTDIPHTHERITIC POLYNEURITIS AND PSEUDODIPHTHERITIC POLYNEURITIS

Report of Two Cases Treated with Cortisone and Corticotropin

H. J. ROBERTS, M.D., West Palm Beach, Fla.

THE SUCCESSFUL treatment of acute polyneuritis due to various known diseases and of the acute polyneuritis of unknown etiology, known as the Guillain-Barré syndrome, has been effectively enhanced by the use of cortisone and corticotropin. The use of these agents has resulted in dramatic and life-saving improvement, but it is still somewhat controversial. Some feel that their prolonged use may break through important antibacterial and antiviral immunologic defenses. The therapeutic problem is further increased when the etiology is obscure. This is particularly so if one is confronted with such a symptom-complex, with or without bulbar involvement, during the poliomyelitis season, when the latter cannot be definitely ruled out—even in the presence of an acellular spinal fluid.

I have recently encountered two patients with a diphtheritic or pseudodiphtheritic polyneuritis in whom the hormones were employed, primarily because of their progressively deteriorating states. Since I have been unable to find any pertinent information or review in the literature concerning this therapy as specifically employed in diphtheritic polyneuritis, this experience is now set forth. It is hoped that this report may serve as a reference to those who may subsequently be confronted with these considerations. The presentation of a negative response in the one proved patient needs no apology; it merely demonstrates the need for the earlier institution of hormonal treatment, if such therapy proves to be fruitful in the hands of others and is decided upon. The other patient, who had ingested apiol and in whom throat cultures were negative, owing possibly to the combination of the long time-interval prior to her seeking medical help and the intervening penicillin therapy, would have been deprived of the salutory effects of cortisone were it not for the fortuitous appearance of a severe penicillin or serum reaction necessitating its use. A brief review of the pertinent diagnostics and current literature relating to this problem is included in the Comment.

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REPORT OF CASES

CASE 1.—A 38-year-old white caretaker was first admitted to the hospital on the ENT service on March 7, 1954. He complained of a severe sore throat of four days' duration and painful swallowing. Examination revealed an extensive grayish membranous exudate over the posterior pharynx, tonsillar areas, and soft palate, with lymphadenopathy. The second of two throat cultures was highly suggestive of diphtheria, and he was transferred to a local contagious disease hospital. He had received penicillin prior to transfer.

At the other hospital three nose and throat cultures were reported as negative for diphtheria and hemolytic Streptococcus. His temperature (106 F) rapidly became normal. The senior physician there did not feel that the patient had a clinical picture of diphtheria, and no antitoxin was administered. He was placed on a course of oxytetracycline (Terramycin) for five days. After 12 days, he was discharged with the diagnosis of acute pharyngitis. Four days after returning home he became aware of ataxia, and a few days later there were numbness, paresthesiae, and some loss of sensation in his hands and forearms, extending to the vicinity of the elbows. His capacity for ambulation became steadily worse.

He was readmitted to the hospital on April 10, 1954, at which time he was unable to walk without

holding on. He complained of hoarseness, difficulty in deglutition, and regurgitation of fluid through his nose. He also complained of hyperesthesia of the left occipital region lateral to a previous skull defect and extending around to the left parietal area. There was some loss of taste, a sensation of rawness of his tongue, soreness in his mouth, and, for the previous 10 days, a blurring of print within two or three minutes after he began to read.

The patient's past history was significant in that he had had lobar pneumonia at the age of 10 and malaria while in Korea. While a prisoner of war, in 1950, he had received four bullet wounds and was forcibly struck in the occiput with a rifle butt, which resulted in a fracture of his skull, with residual unconsciousness for three weeks. Over the ensuing two years, he had regained 25% vision in the left eye but none in the right temporal or left nasal fields.

Physical Examination.—Height, 5 ft. 4 in.; average weight, 160 lb.; maximum weight, 165 lb.; present weight, 135 lb. Temperature, 98.6 F; pulse rate, 84; respiration rate, 20; blood pressure, 116/78. The patient appeared normally developed and nourished, although he had lost 20 lb. His voice was hoarse. He complained of pins-and-needles sensations and weakness of the hands and arms, together with unsteadiness of his feet. There was a bony defect in the left occiput, the site of a previous decompression operation, and some anesthesia immediately surrounding this, with hyperesthesia extending to the left and over the temporoparietal area. A few spider angiomata were present on the nose and malar areas. There was no cervical or supraclavicular adenopathy. On extreme forward flexion of the neck, he complained of some stiffness. The pupils were slightly irregular; the right was slightly larger than the left, but both reacted to light. The eye movements were normal in all directions. There was a right homonymous hemianopsia. The nasal septum deviated to the left, and the tongue protruded slightly to the right. Both palatal folds moved equally. The head and lungs were not remarkable.

The patient walked with a rather rigid wide gait, definitely unsteady, and markedly so when attempting to turn. All reflexes, including the abdominal ones, were absent. Vibratory sense was absent. The Babinski response was plantar. Strength was equally good in the hands and in the biceps and triceps, but the patient insisted that the results were definitely weak for him. There was good and equal strength in both legs. Past pointing was present on the left side. The Romberg test was positive. Light touch and pain sensation were present in all limbs. There was no astereognosis.

Laboratory Data.—WBC, 12,100, with 75% polymorphonuclear cells and 25% lymphocytes. Hgb., 15 gm. per 100 cc. Results of urinalysis and serologic studies were normal. Three throat cultures were now negative for diphtheria and revealed a predominating β-hemolytic Streptococcus. The blood culture was negative. A lumbar puncture revealed normal pressures and clear fluid with sugar, 78 mg/100 cc.; total protein, 32 mg/100 cc.; a trace of globulin, and negative colloidal gold and serologic tests. A chest film was normal. Skull films showed a large bony defect just to the left of the external occipital protuberance; the pineal gland was calcified in the midline. The electrocardiogram revealed depressed ST segments in Leads I and II, inverted T waves in Leads I and aV_L and V_6; it was considered to be consistent with myocarditis. An electroencephalogram was interpreted as abnormal, with a lack of rhythmicity in the left occiput; this was felt to be in keeping with the patient's war injury and was not ascribed to his recent illness.

Course in the Hospital.—In the belief that the patient had developed a fairly typical postdiphtheritic polyneuritis and paralysis and in view of both the paucity of literature and the experience in Case 2, hormonal therapy was instituted. Intramuscular cortisone acetate was begun on April 16 in daily dosages of 100 mg. and was discontinued on April 21 in favor of daily intravenous corticotropin, 20 mg., over eight-hour periods. A total of 11 days of hormonal therapy was given. Daily electrocardiograms during this time showed no change from the original admission tracing. Cyanocobalamin (vitamin B_{12}), 500γ daily, was added, along with erythromycin, 200 mg. every six hours for seven days.

Despite the aforementioned medication, the paresis and cardiac rate increased during the first two weeks. By April 26 he was no longer able to hold a spoon, his voice had become hoarser, and the regurgitation of fluid through his nose continued. Respiratory movements were unimpaired. By May 3 he complained of numbness of the buttocks, increased sensory loss of the hands and arms, and increased weakness of the shoulder girdles, arms, and legs. By May 13 all power had been lost to the extensors of his fingers. By May 17 his forearms were useless and it was necessary to feed him.

On April 21 the consulting neurologist made a diagnosis of a generalized polyneuritis resulting from bacterial infection (probably diphtheria). The patient was reexamined on April 30, at which time it was noted that the polyneuritis had extended and involved a greater number of the peripheral nerves. The eye consultant noted paresis of the ciliary muscles of both eyes. An ENT consultant reported diminished activity of the left side of the larynx and palate. By May 7 the patient's weight

had dropped to 132 lb. Reconditioning exercises were begun on May 24, at which time his swallowing and voice had improved but the arms and forearms were very weak. By June 7 his swallowing and voice were practically normal, and on June 14 it was apparent that the function of his arms and legs was slowly returning. The patient was discharged home on July 26, with the diagnoses of polyneuritis, generalized, postdiphtheritic, and myocarditis, toxic, postdiphtheritic.

CASE 2.—A 27-year-old white married woman was admitted by emergency air flight with the tentative diagnosis of bulbar poliomyelitis. Two weeks prior to admission she had had a severe sore throat, for which she received no treatment and which had subsided considerably during the course of the ensuing weeks. Five days prior to admission she noted the onset of fleeting painful sensations in the tips of her fingers and heels, described as "a thawing-out sensation, such as after freezing my fingers." Three days prior to admission the sensation recurred and lasted for two hours. That evening, she developed difficulty in talking and noted the development of a nasal quality to her speech. Shortly thereafter she experienced increasing difficulty in swallowing and numbness in both legs. She was admitted to another hospital, where she was found to have pharyngeal and bilateral painful paralysis, associated with a generalized areflexia. An exudate on the right tonsil was described. She received 40,000 units of diphtheria antitoxin and 500,000 units of penicillin intramuscularly; later, cultures for diphtheria organisms were taken. A spinal tap was done and was completely within normal limits, the protein being 26 mg/100 cc., with no cells noted. The following day she complained of increasing generalized weakness and was unable to support herself even in bed. No sphincter symptoms or diplopia were admitted. In view of the rapid progression of her weakness and increasing respiratory difficulty, she was transferred to this larger center.

The past history was significant only in that 10 days previously she had taken two capsules of "Ameco" as an abortifacient. Each of these capsules contained ergot (0.3 gm.), aloin (15 mg.), apiol (5 mg.), cottonseed oil, and sesame oil. No recent contact with either poliomyelitis or other infectious diseases was known. The other members of her family were well. No pork or questionable meat had been ingested recently. As a child, she had received the usual immunizations and one diphtheria booster injection when she started school.

Physical Examination.—Examination on admission revealed a young white woman in acute respiratory distress, with a frequent weak cough. She complained of general weakness, most marked in the right limbs. There was a marked nasal quality to her voice, and she could be understood only with difficulty. She appeared to be alert, however, and oriented in all spheres. Considerable difficulty was experienced in expectorating the secretions from the posterior pharynx. She was afebrile. Blood pressure was 114/76; pulse rate, 110 and regular; respirations, 24 to 28 per minute. A generalized muscular weakness was manifest. She was unable to sit up and could turn in bed only with the greatest effort. Slight oropharyngeal and nasal injection were seen, but there was no suggestion of a membrane. Examination of the neck, chest, heart, lungs, and abdomen was not remarkable except for the tachycardia. No adenopathy was present.

Neurological examination revealed the following: The pupils were round, regular, and equal and responded to light; hippus was present; accommodation was impaired in both eyes, most markedly on the right; the fundi appeared normal; movement of the eyes in all directions was impaired; bilateral ptosis of the eyelids was present. There was a generalized weakness of the other facial muscles, the neck and jaw muscles, and of all the peripheral voluntary muscles, especially those of the right limbs. A palatal paralysis was present bilaterally. Areflexia was generalized except for weak triceps reflexes. Vibratory sensation was decreased in the hands. Finger-to-nose testing resulted in a marked intention tremor and past pointing. The other sensory modalities tested were not remarkable. No pathological reflexes were elicited; the superficial reflexes were unaltered.

Laboratory and Other Examinations.—Blood studies revealed a white cell count of 14,100, with 77% neutrophiles and 22% lymphocytes. Hematocrit value was 44%; RBC, 4,320,000. No atypical lymphocytes or stippling of the red cells was noted. Repeated urinalyses were all essentially within normal limits. Several cultures (after penicillin) taken and those at the first hospital from the nose, the oropharynx, and the tracheal secretions were all negative for Corynebacterium diphtheriae. It was decided not to perform a Schick test initially, since antitoxin had recently been administered. A spinal puncture revealed a clear, colorless fluid under no increased pressure; there were two lymphocytes per cubic millimeter and 63 mg. sugar and 17 mg. protein per 100 cc. Both the blood and the spinal fluid were seronegative. Routine throat cultures grew out Hemophilus influenzae. Repeated blood studies for heterophile agglutinins and viral antibodies were subsequently reported as negative. An electrocardiogram revealed only a sinus tachycardia. Screening tests for urinary porphyrins were negative. In order to rule out acute myasthenia

gravis, a test dose of neostigmine was given shortly after admission; no clinical response was noted.

Clinical Course.—The patient's course during her first week of symptomatic care was one of a progressive aggravation of her muscular weakness, dysphonia, and dysphagia. In order to maintain her nutrition, she received a 2100 Cal. diet via a gastric tube. Neither pencillin, cyanocobalamin, supplementary vitamins, nor tripelennamine (Pyribenzamine) was clinically effective in staying the advance of the polyneuritis. The use of cortisone or corticotropin was intermittently suggested, but the consultants on both the medical and neurological services who saw the patient were opposed to their administration.

Seven days after admission the patient developed a severe generalized urticarial eruption with an associated low-grade fever. Joint symptoms were minimal. Although this was considered to be a penicillin reaction, a reaction to the previously administered antitoxin could not be ruled out. In view of her truly critical status, she was started on intramuscular cortisone acetate, 100 mg. thrice daily. Within 24 hours she had begun to experience some improvement in her motor ability, had noted a lessened ptosis of her eyelids, and found she was beginning to swallow successfully. The urticaria also abated dramatically.

She was maintained on 300 mg. of cortisone for two days; the dose was then reduced to 100 mg. daily over a period of three days. A repeat spinal tap revealed an essentially normal and acellular spinal fluid except for a protein content of 53 mg/100 cc. (normal in the laboratory is up to 45 mg.). The rapid increase in muscular tone and improvement in muscular function continued. She was kept on bed rest in order to prevent or minimize an ensuing myocarditis; repeat electrocardiograms remained within normal limits. After a total of 10 days of cortisone therapy, during which time the dosage had been gradually reduced, cortisone was discontinued. A Schick test was now negative. Although ocular accommodation appeared normal and no reading difficulties were experienced during convalescence, the ophthalmologist again detected ciliary paresis. During the patient's last week in the hospital she regained practically complete function of the voluntary muscles, as tested by the physical therapist. Follow-up examination three months after discontinuation of cortisone revealed no recurrence of symptoms, even on full activity.

COMMENT

Differential Diagnosis of Atypical Diphtheritic Polyneuritis

The diphtheritic etiology of the polyneuritis in Case 1 was confirmed by culture; this was not so in Case 2, owing possibly to the absence of the organism on culture following the previous penicillin therapy. The diagnostic importance of a diphtheritic polyneuritis asserted itself in the second case, notwithstanding the atypical earlier onset and the rapid progression of the palatal and muscular paralysis. The ciliary involvement is generally regarded as being fairly specific for this disorder. In reference to the problem of negative cultures, Edwards found the initial throat culture to be positive in only 60% of 100 patients dying with diphtheria.[5] Interestingly, albuminocytologic dissociation occurs in a high percentage of patients with a delayed diphtheritic polyneuritis.* The fact that persons who receive the usual diphtheria immunizations in childhood may not be subsequently completely protected against the disease, particularly in the older age groups, is becoming increasingly appreciated.† One should keep in mind that a physician with the extensive experience of Place has stressed that the concept of antitoxic immunity in Schick-negative persons has often been too dogmatic and that the immunity is only relative.[13] Brown has pointed to the increasing number of patients seen with diphtheritic polyneuritis since the antibiotics became available. The wisdom of antitoxin administration in situations such as both patients initially presented cannot be argued.

Acute bulbar poliomyelitis can be ruled out only with difficulty in a community where individual cases of the disease are still being reported. This was a consideration in the second patient. It would appear from the persistently acellular spinal fluid and the subsequent course of the illness that this disease was not present. Aside from matters of prognosis and epidemiology, this consideration is one of great importance where hormonal therapy is being considered. Although Ainslie and co-workers[2] could not show definite acceleration of the disease with either corticotropin or cortisone in white mice and

* References 6-8.

† References 9-12.

rhesus monkeys, other investigators and clinicians are convinced that this does occur.[3] The other common viral and rickettsial neurotropic organisms producing specific antibodies in convalescent blood specimens, particularly that of mumps, were also unlikely factors in this case.

A polyneuritis due to the ingested apiol, even in such a small amount, was considered as being possible. Although its use is infrequent nowadays, it was frequently employed at one time in the treatment of dysmenorrhea and other uterine disorders; in this case, it was used as an abortifacient. Chemically, it is 1-allyl-2,5-dimethoxy-3,4-methylene dioxybenzine, which when oxidized becomes apiolic acid. It is primarily a hepatotoxin, but it has also been noted to produce a polyneuritis and to have a direct weakening action on the voluntary muscles.[4]

After such entities, which occasionally are responsible for a polyneuritis, as porphyrinuria, diabetes mellitus, infectious mononucleosis, various poisonings, and nutritional deficiencies were ruled out, the diagnosis of the pleomorphic entity variously referred to as the Guillain-Barré syndrome, infectious polyneuritis with facial diplegia, infectious neuronitis, radiculomyelitis, and acute febrile polyneuritis was considered. Most authors have described a symptom-complex characterized by paraesthesias, muscle pain, and rapidly progressive motor weakness, often following a respiratory illness. The diagnostic problem created by acute infectious polyneuritis during a poliomyelitis epidemic may be considerable, as shown by De Sanctis and co-workers.[1] Sensory changes, when present, are usually overshadowed by such motor symptoms as flaccid paralysis, dysphagia, bladder and bowel involvement, and respiratory paralysis. The most convincing arguments against such a diagnosis in the second case are twofold, namely, the ciliary muscle paralysis and the normal or very slightly elevated spinal fluid protein levels on three occasions.

Therapeutic Considerations with Cortisone and Corticotropin

Case reports have been accumulating in the literature which indicate the significant reduction in both morbidity and mortality produced by the administration of these hormones to patients with polyneuritis of various etiologies. Several such reports dealing with the Guillain-Barré syndrome have appeared.‡ It should be appreciated that the disease usually increases in both extensiveness and severity for two to six weeks and that from 20% to 42% of patients may die during this phase, usually from respiratory paralysis. Another consideration of note is that while complete recovery from even an extensive paralysis is the rule, provided the patient can be successfully nursed through this period, it is usually a matter of weeks or months.[20] Since patients with paralysis usually tend to remain clinically stationary for some weeks before spontaneous improvement occurs, a prompt remission such as is described in the second case must be considered as being due to the hormonal therapy. Subsequent exacerbations have been noted as long as 10 weeks after the induced remission; these relapses will usually respond again to cortisone or corticotropin. It would appear, therefore, that if hormonal therapy is decided upon it should be continued for at least three weeks. That universal benefit cannot be expected is evident by the report of Grant and Leopold, who observed the development of this syndrome in a patient receiving large doses of cortisone for rheumatoid arthritis.[21]

Pathologically, the important role of edema of the nerve roots—with secondary compression of the inelastic dural sheaths, myelin degeneration, and beading of the axones—in disrupting nerve function has been emphasized.§ The cause of this edema is obscure; several authors have stated that in some cases it may represent an "allergic response of the

‡ References 15-19.

§ References 22 and 23.

nervous system," especially to bacterial products.‖ Associated changes in the anterior horn cells, brain stem, and even the cerebral hemispheres are usually considered as secondary. The striking improvement with hormonal therapy is attributed to the resorption of this edema and subsequent decompression. It is possible that the edema may be responsible for the elevated spinal fluid protein level by preventing the resorption of the larger protein molecules through the perineural spaces of the cranial nerves and the spinal nerve roots.[24] The prompt drop in spinal fluid protein sometimes seen concomitantly with a hormone-induced remission is a distinctly unusual occurrence in untreated cases.[25] It is generally conceded, however, that the improvement from such treatment, when it occurs, is nonspecific.

Experienced clinicians can readily cite the prolonged morbidity that occasionally is produced by the polyneuritis and encephalitis of infectious mononucleosis. Two striking case reports of prompt remissions have appeared, one with corticotropin [26] and the other with cortisone.[27] Garrison has described amelioration of the encephalomyelitis induced by antirabies vaccination when cortisone was used.[28] This clinical suppression of postvaccinal neurological reactions receives laboratory support from the work of Kabat and co-workers [29] and Moyer and his colleagues.[30] They were able to suppress a demyelinating encephalomyelitis in experimental animals by pretreatment with either agent. It was felt that the mode of action lay in the modification of the local granulomatous response, previously shown to be necessary for the production of the disseminated encephalomyelitis. The importance of this problem, for which no therapy had been heretofore successful, can be inferred from the report of Appelbaum and his colleagues, who cite the incidence of neurological complications to be 1 out of 2025 persons receiving the vaccine.[31]

There is also increasing evidence that localizing neuritides may respond clinically to these hormones. One of the most important milestones has been the successful treatment of acute optic and retrobulbar neuritis, occurring either as a manifestation of multiple sclerosis or as an independent phenomenon.¶ Quinn and Wolfson have emphasized the fact that prolonged treatment at high dosage levels may even be effective in chronic and apparently irreversible cases of optic neuritis. [34] Similarly, the initial skepticism concerning the use of cortisone in Bell's palsy following the initial reports has waned in the face of an increasing number of cases, primarily acute, in which recovery has occurred.# Its beneficial action is assumed to be due to a reduction of the congestion and secondary ischemia of the nerve and its sheath in the bony canal.

Concerning the present issue of the effect of these hormones in patients with postdiphtheritic polyneuritis and paralysis, I have been unable to find reports relating to their use in this entity. Two papers have inferred that they "should be effective."* The reasons for such an absence may be twofold. First, individual cases may not have responded and the negative results were not considered "reportable." Secondly, a reluctance to employ these agents may have resulted from several experimental studies. It should be remembered that the diphtheria toxin, considered a prototype exotoxin, is probably fixed in an indissociable bond at its site of action. Whether hormonal influence can modify this cellular response, which antitoxin is unable to do, is the crux of the problem.

Rosenbaum and Obrinsky,[40] investigating the effects of cortisone on diphtheria intoxication and the Schick test in guinea pigs, have reported the following results:

1. Cortisone did not affect the development of positive Schick reactions in non-immunized guinea pigs. 2. Cortisone did not prevent death, significantly increase survival time or prevent adrenal hemorrhages in guinea pigs given diphtheria toxin. 3. Cortisone did not interfere with the protective action

‖ References 15-17.

¶ References *32* and *33*.

References 35-38.

* References 14 and *37*.

of diphtheria antitoxin in guinea pigs given diphtheria toxin. 4. Cortisone had no direct neutralizing effect on diphtheria toxin *in vitro*.

Brainerd and Scarparone also found that cortisone neither retarded nor accelerated the lethal effect of the toxin in guinea pigs and that it did not prevent the neutralization of diphtheria toxin by previously induced passive antitoxic immunity.[41] That neither cortisone nor corticotropin interferes with active diphtheria antitoxin production to diphtheria toxoid, even in persons with extensive acute and chronic liver disease, has been conclusively shown by Eichman and Havens.†

It is apparent in the case of the first patient herein reported that an 11-day course of hormonal therapy, possibly in somewhat small dosage, was ineffectual in either reversing or retarding the diphtheritic polyneuritis. If the polyneuritis in Case 2 was due to diphtheria, the prompt remission was indeed remarkable. Brown has stated that the average time of recovery is three months.[14] She feels that the polyneuritis represents an allergic response of the nerve cell to a foreign substance rather than the direct action of the toxins on the nerves. This is implied by the length of time before the onset of even the palatal paralysis and by the mild local paresis produced when the toxin is injected intraneurally rather than intravenously.

Perhaps the entire salutory therapeutic response in a patient with diphtheritic polyneuritis is related to the prompt administraton of cortisone and corticotropin when the development of this complication seems very likely. Recently, Favour and his colleagues have reported their detailed studies of this very factor in evaluating the effect of cortisone on the survival of guinea pigs inoculated with diphtheria toxin.[44] They found that increased longevity was effected if the cortisone was begun in the first five days, presumably owing in large measure to the amelioration of the effects of the crippled cytochrome system of respiration by delay of cellular anabolic and catabolic activities. It was equally significant that cortisone given later than six days after the dose of toxin increased the number of fatalities.

† References 42 and 43.

SUMMARY AND CONCLUSIONS

The experience in the treatment of two cases of diphtheritic and pseudodiphtheritic polyneuritis with cortisone and corticotropin is presented, owing to the paucity of such information in the literature.

In one patient with atypical diphtheritic polyneuritis these hormones neither reversed nor retarded the neuritis and cardiac complications. The treatment had been delayed, however, by one month following the initial pharyngitis.

The other patient manifesting a progressive neuritis exhibited a dramatic and complete remission when cortisone was begun, approximately three weeks after the faucial inflammation and two weeks after she had ingested apiol. The diphtheria organism was not cultured, although penicillin and antitoxin therapy had already been administered. The differential diagnosis of this case is discussed.

The available literature relating to the use of cortisone and corticotropin in diphtheria and polyneuritis is reviewed.

It is suggested that serious consideration be given to the employment of these agents in patients with progressive polyneuritis, particularly when bulbar symptoms are present and the etiology is obscure. It is stressed that the definitive place of hormonal therapy instituted early in diphtheritic polyneuritis has yet to be evaluated.

Dr. Donald Gates provided many details of the first case, and Dr. Louis Weinstein made suggestions.

REFERENCES

1. De Sanctis, A. G.; Adolph, G., and Green, M.: Acute Infectious Polyneuritis: A Diagnostic Problem During a Poliomyelitis Epidemic, J. A. M. A. **118**:1945, 1942.

2. Ainslie, J. D.; Francis, T., Jr., and Brown, G. C.: ACTH in Experimental Poliomyelitis in Monkeys and Mice, J. Lab. & Clin. Med. **38**:344, 1951.

3. Shwartzman, G.: Enhancement of Susceptibility to Experimental Poliomyelitis by Means of Cortisone, Am. J. Path. **27**:714, 1951.

4. Osol, A., and Farrar, G. E., Jr.: The Dispensatory of the United States of America, Philadelphia, J. B. Lippincott Company, 1950, p. 1543.

5. Edwards, W. M.: Analysis of Fatal Cases of Diphtheria, U. S. Armed Forces M. J. **2**:217, 1951.

6. Copsey, H. G.: Postdiphtheritic Paralysis, M. Clin. North America **30**:445, 1946.

7. Delp, M. H.; Southerland, G. F., and Hashinger, E. H.: Post-Diphtheric Polyneuritis, Ann. Int. Med. **24**:618, 1946.

8. Bronson, L. H.: Neurologic Disease Following Infections of Throat and Skin and Incidence of Diphtheric infections, Arch. Neurol. & Psychiat. **56**:558, 1946.

9. Brainerd, H. D.; Kiyasu, W.; Scaporone, M., and O'Gara, L.: Susceptibility to Diphtheria Among Elderly Persons: Immunization by Intracutaneous Administration of Toxoid, New England J. Med. **247**:550, 1952.

10. Edward, D. G., and Allison, V. D.: Diphtheria in the Immunized with Observations on Diphtheria-like Disease Associated with Non-Toxigenic Strains of Corynebacterium Diphtheriae, J. Hyg. **49**:205, 1951.

11. Merkel, A. E.: An Outbreak of Diphtheria in Medford, Oregon, Am. J. Pub. Health **41**:522, 1951.

12. Edsell, G.: Active Immunization, New England J. Med. **241**:18, 1949.

13. Place, E. H.: Present Status of Diphtheria, Ann. Otol. Rhin. & Laryng. **56**:347, 1947.

14. Brown, M. R.: The Mechanism Involved in Polyneuritis as Exemplified by Postdiphtheritic Polyneuritis, Ann. Int. Med. **24**:786, 1946.

15. Stillman, J. S., and Genong, W. F.: The Guillain-Barré Syndrome: Report of a Case Treated with ACTH and Cortisone, New England J. Med. **246**:293, 1952.

16. Newey, J. A., and Lubin, R. I.: Corticotropin (ACTH) Therapy in the Guillain-Barré Syndrome, J. A. M. A. **152**:137, 1953.

17. Blood, A.; Locke, W.; and Carabasi, R.: Guillain-Barré Syndrome Treated with Corticotropin (ACTH), J. A. M. A. **152**:139, 1953.

18. Seltzer, H. S.; Lichty, D. E., and Conn, J. W.: A Case of the Guillain-Barré Syndrome (Infectious Polyneuronitis) with Apparent Response to ACTH, Univ. Michigan M. Bull. **18**:27, 1952.

19. Plum, F.: Multiple Symmetrical Polyneuropathy Treated with Cortisone, Neurology **3**:661, 1953.

20. Brain, W. R.: Diseases of the Nervous System, Ed. 3, New York, Oxford University Press, 1947, p. 795.

21. Grant, H., and Leopold, H. N.: Guillain-Barré Syndrome Occurring During Cortisone Therapy, J. A. M. A. **155**:252, 1954.

22. Roseman, E., and Aring, C. D.: Infectious Polyneuritis, Medicine **20**:463, 1941.

23. Scheinker, I. M.: Pathology and Pathogenesis of Infectious Polyneuritis, J. Neuropath. & Exper. Neurol. **8**:184, 1949.

24. Reitman, N., and Rotschild, K.: Non-Infectious Nature of Guillain-Barré Syndrome with Possible Explanation for Albumino-Cytologic Dissociation, Ann. Int. Med. **32**:923, 1950.

25. Forster, F. M.; Brown, M., and Merritt, H. H.: Polyneuritis with Facial Diplegia, New England J. Med. **225**:51, 1941.

26. Hubler, W. L.; Bailey, A. A.; Campbell, D. C., and Mathieson, D. R.: Infectious Mononucleosis with Predominantly Neurologic Manifestations: Report of a Case, Proc. Staff Meet. Mayo Clin. **26**:313, 1951.

27. Piese, M. J.; Cheu, S., and Radding, J.: Guillain-Barré Syndrome in Infectious Mononucleosis: Report of a Case with Recovery Following Administration of Cortisone, A. M. A. Arch. Int. Med. **92**:438, 1953.

28. Garrison, S. C.: Encephalomyelitis Complicating Antirabies Vaccination Treated with Cortisone, Am. J. Med. **12**:135, 1952.

29. Kabat, E. A.; Wolf, A., and Bezr, A. E.: Effect of Cortisone on Experimental Acute Disseminated Encephalomyelitis, Fed. Proc. **10**:412, 1951.

30. Moyer, A. W., and others: Action of Adrenocorticotropic Hormone (ACTH) in Experimental Allergic Encephalomyelitis of Guinea Pig, Proc. Soc. Exper. Biol. & Med. **75**:387, 1950.

31. Appelbaum, E.; Greenberg, M., and Nelson, J.: Neurological Complications Following Antirabies Vaccination, J. A. M. A. **151**:188, 1953.

32. Smith, E.: Bilateral Optic Neuritis Treated with Intravenous Administration of Corticotropin, A. M. A. Arch. Ophth. **48**:522, 1952.

33. Gordon, D. M., and others: Use of ACTH in Ophthalmology, in Proceedings of the Second ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 457.

34. Quinn, J. R., and Wolfson, W. Q.: Improved Results from Intensive Hormonal Treatment in Certain Eye Diseases Reported to Respond Poorly to ACTH or Cortisone, Univ. Michigan M. Bull. **18**:1, 1952.

35. Rothandler, H. H.: Bell's Palsy Treated with Cortisone, J. Nerv. & Ment. Dis. **114**:346, 1951.

36. Rothandler, H. H.: Bell's Palsy Treated with Cortisone, Am. J. M. Sc. **225**:358, 1953.

37. Robbins, M. H.: Bell's Palsy Successfully Treated with Cortisone, A. M. A. Arch. Ophth. **48**:696, 1952.

38. Robinson, W. P., and Moss, B. F.: Treatment of Bell's Palsy with Cortisone, J. A. M. A. **154**:142, 1954.

39. Reimann, H. A.: Infectious Diseases: Eighteenth Annual Review of Significant Publications, A. M. A. Arch. Int. Med. **91**:353, 1953.

40. Rosenbaum, P., and Obrinsky, W.: Effect of Cortisone on Diphtheria Intoxication and the Schick Test in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **83**:502, 1953.

41. Brainerd, H., and Scaparone, M.: The Effect of Cortisone on the Fixation and Neutralization of Diphtheria Toxin, Antibiotics & Chemother. **3**:696, 1953.

42. Eichman, P. L.; Havens, W. P., and Miller, R. W.: The Effect of ACTH and Cortisone on the Concentration of Circulating Antibody in Patients with Acute Hepatitis, J. Clin. Endocrinol. **13**:648, 1953.

43. Havens, W. P.; Shaffer, J. M., and Hopke, C. J., Jr.: The Effect of ACTH and Cortisone on the Concentration of Circulating Diphtheria Antitoxin, J. Immunol. **68**:389, 1952.

44. Favour, C. B.; Atlas, L. T.; Levine, M. I., and Osgood, C. K.: The Effect of Cortisone on the Survival of Guinea Pigs Inoculated with Diphtheria Toxin, Lab. Invest. **3**:1, 1954.

RENAL DISEASE, INNER EAR DEAFNESS, AND OCULAR CHANGES

A New Heredofamilial Syndrome

EZRA SOHAR, M.D., Tel-Aviv, Israel

A CLINICAL syndrome characterized by progressive deafness, ophthalmological changes, and laboratory evidence of chronic renal disease has been observed and studied in four brothers. The results of clinical and laboratory investigations conducted while these patients were hospitalized yielded an almost identical picture in all four siblings. At the time of investigation, their ages were 18 (J.), 17 (I.), 16 (N.), and 14 (M.).

In all instances, deafness was first noted at age 9 to 10 and was progressive. The youngest brother (M.) in addition had had intermittent back pain since the age of 12 (once with hematuria?) and amebic colitis at the age of 13.

Physical examination in all instances revealed normal physical development, asthenic build, long extremities and fingers, and high palate. Their weights ranged from 55 kg. in the oldest to 40 kg. in the youngest. An apical systolic murmur was audible in all except N. A positive Graefe sign was noted in J. and M. M. had moderate hepatosplenomegaly, while in I. only splenomegaly was present.

The renal studies are summed up in Table 1.

In all four brothers there was evidence of chronic renal disease, manifested by large amounts of protein, erythrocytes, leucocytes, and granular casts in the urine; moderate elevation of the blood urea nitrogen; substantially decreased urea clearance, and decreased urine concentrating power. The two elder brothers had slight hypertension, and I. and M. had abnormal electrocardiograms. There were no signs of a nephrotic syndrome—no edema, normal serum proteins (determined by chemical methods and paper electrophoresis), and normal serum cholesterol levels. In one patient a rectal biopsy for amyloidosis and Congo red test were negative. The amino acids in the urine showed normal patterns on paper chromatography—excluding the group of renal diseases associated with abnormal amino-aciduria. Urinary output was normal and repeated urine cultures were sterile in all instances. Intravenous pyelography revealed normal structures and function in all four patients.

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Department of Medicine, Tel-Hashomer Government Hospital; Present Address: The Mount Sinai Hospital, New York.

TABLE 1.—*Renal-Function Studies*

	Patient J	Patient I	Patient N	Patient M
Urine protein, gm./100 cc.	2.5	4-10.7	2.5-6	4.5-10
Urine erythrocytes	2-3	+	Few	++
Urine leucocytes	2-3	+	Few	+
Urine granular casts	++	+	+	Few
Urine concentration-dilution	?	1001-1010	1001-1018	1001-1019
Electrophoresis of urine protein	?	Albumin and some β-globulin	?	Albumin and some β-globulin
Blood urea nitrogen, mg./100 cc.	40-51	50	45	33
Urea clearance test (1, 2, mean)	42, 20, 31	62, 69, 65.5	31, 43, 37	32, 36, 34
Total serum protein, gm./100 cc.	7.3	6.0	5.3	5.6
Albumin, gm./100 cc.	4.8	3.6	3.6	4.0
Globulin, gm./100 cc.	2.5	2.4	1.7	1.6
Blood pressure	135/75	150/90	110/70	110/75

TABLE 2.—*Auditory Studies*

	Patient J	Patient I	Patient N	Patient M
Otoscopy	N	N	N	N
Audiometry				
Air	125-500, loss of 40 db. (approx.) 1,000-8,000, loss of 70-80 db. (approx.)			
Bone	Same findings; loss somewhat greater			
Recruitment	+	+	+	+
Caloric tests	N	N	N	N
Beginning of deafness (age, yr.)	9-10	9-10	10-11	10-11
X-ray (Schiller)	N	N	N	Incomplete pneumatization

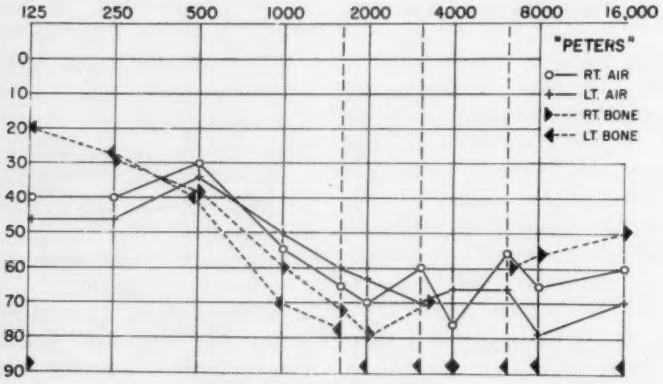

Fig. 1.—Audiogram.

TABLE 3.—*Ophthalmologic Changes*

	Patient J	Patient I	Patient N	Patient M
Vision, O.D.	6/60—3.5=6/36	1/9—6.0=6/20	6/12—2=6/9	1/6—5=6/18
Vision, O.S.	6/60—3.7=6/36	1/5—6.0=6/20	6/18—3=6/9	1/6—3=6/12
Spherophakia	+	+	—	—
Fundus examination	Atrophia choroideae	N	N	Atrophia retinae, blurred papilla
Astigmatism	+ (lenticular)	—	—	+
Congenital posterior cortical cataracts	—	+	—	+
Perimetry	N	N	N	N

Ears.—Investigations of auditory function revealed even more pronounced resemblances among the brothers (Table 2). In all four, otoscopy showed no abnormalities. Audiometry showed a loss of 40 db. at 125 to 500 cps and of 70 to 80 db. at 1000 to 8000 cps in air and bone. A typical audiogram is depicted in Figure 1. Recruitment was positive. Caloric tests were normal. X-ray studies were normal in all except M., in whom incomplete pneumatization was noted. These findings, particularly the positive recruitment, are typical of isolated inner ear deafness without lesions of the labyrinth or acoustic nerve.

Eyes.—The ophthalmological changes in the four patients are depicted in Table 3. All had myopia of medium grade (3 to 6 D.), but none presented a myopic fundus. In the two elder brothers spherophakia was the cause of the myopia. Two brothers had congenital posterior cortical cataracts.

Spherophakia is a malformation caused by sudden arrest of development of the lens. Most authors state that the immediate cause is an aplasia of Zinn's zonule. The zonule fibers, being feeble, are unable to exert the usual pull on the periphery of the lens, and as a result the lens keeps its fetal, round form. Some authors believe that the arrest in the

development of the lens occurs mainly after the age of 10.[2] The relation between ectopy of the lens (which occurs often as part of Marfan's syndrome) and spherophakia is evident: in ectopy of the lens the fibers of Zinn's zonule are aplastic in one segment only, while in spherophakia the aplasia is total and comprises the fibers all around the lens.[3] This lack of centrifugal force causes the diameter of the lens to be relatively small, a phenomenon known as microphakia and described only in combination with spherophakia. The increased sagittal diameter of the lens causes myopia. Spherophakia is rare, with only 28 cases published up to 1953. It is considered a hereditary malformation, sometimes associated with consanguinity. Merchesani [4] and, later, other authors [5] have described instances of spherophaika in combination with brachidactyly and have suggested that this combination should be known as a hyperplastic form of mesodermal dystrophy, as opposed to Marfan's syndrome, which they consider the hypoplastic form (lenticular ectopy, long feet and hands, poor development of muscle and fat tissue, and dolichocephalic skull). Our patients more closely resembled the Marfan's syndrome type (asthenic, thin, long extremities, high skull). These features did not, however, exceed normal limits.

No other instances of spherophakia associated with a general disease or any other signs or symptoms (except brachidactyly) have been reported previously. Other examinations and findings included the following: Electroencephalogram, which was normal in three brothers; J. showed a slight nonspecific disturbance. X-rays of skull, chest, and long bones, which were normal. Normal liver-function tests, negative serological tests. Normal plasma and urine electrolytes (Na, K, Cl, Ca, P). Normal hemograms, with absence of fetal hemoglobin. The erythrocyte sedimentation rate was elevated in three brothers (M., 22/44; N., 16/37; I., 28/52; Westergren method).

Because it was evident that we were dealing with a familial disease, an attempt was made to examine a maximum number of family members in order to establish the nature of the genetic transmisison of the syndrome. The family immigrated to Israel from Iraq in 1950. There were two sisters (B., age 9, and L., age 3). Another sister had died at the age of 6 months of unknown cause. The urine of the older sister contained protein, erythrocytes, leucocytes, and granular casts.

The father, aged 56, was normal on physical examination except for myopia of 5 D. and a myopic fundus. There was no deafness and no abnormal urinary findings. His mother, four brothers, and three sisters were alive and in good health.

FAMILY TREE

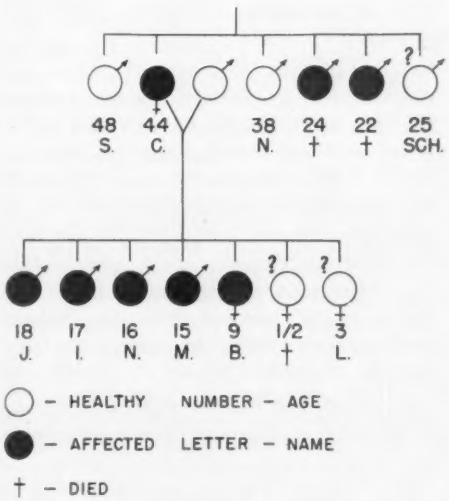

Figure 2

The mother had five brothers, two of whom (S., 48 years old, and N., 38 years old) were examined. No abnormality was found on physical examination or urinalysis. No hearing defects were detected. The youngest brother (Sch., 25 years old) remained in Iraq and so was not investigated. Two other brothers had died in Iraq, one at age 24, the other at 22. Both had progressive deafness from youth and two years before death had developed intermittent fever, weakness, and vomiting. The attending physicians had told

several family members that the brothers had succumbed to a kidney disease. It was not known whether these persons had any visual disturbances or abnormalities.

A family tree is depicted in Figure 2. It shows that in the generation of our four patients one sister was also affected and that in the preceding generations a combination of deafness and renal disease was observed in the mother and two of her brothers, who succumbed to the disease.

These data do not permit any conclusions as to the exact method of hereditary transmission of the multiple defects involved in the syndrome.

COMMENT AND SUMMARY

The clinical picture described is surprisingly similar in all the four patients who were extensively studied and, according to the history, in their two deceased uncles. There was chronic renal disease with abundant excretion of protein, blood cells, and casts in the urine; decreased power of urinary concentration, and defective urea clearance. The deafness was typical of an inner ear lesion, beginning approximately at age 10. All had ophthalmological changes, namely spherophakia (two patients) and congenital posterior cortical cataracts (two patients). The patients were asthenic, with long extremities and fingers.

It is of interest that the deafness beginning at age 10 was associated with spherophakia which, according to some authors, is an anomaly which appears also after this age.

I cannot attribute the syndrome to any (known) error of metabolism, as extensive studies failed to yield any such abnormality.

Spherophakia is known to be a famalial anomaly; familial cases of inner ear deafness have also been described; nephritis can in rare cases attack more than one member of a family; however, the combination of spherophakia, deafness, and renal disease in the form present in this family is striking and has not been described previously. I am unable to explain the connection between the various findings or to suggest an eitologic or pathogenetic explanation.

Dr. I. Shapira, the family's physician, cooperated in this study, and Dr. Elaine T. Bossak, New York, helped in the preparation of the paper.

REFERENCES

1. Sohar, E.: A Heredo-Familial Syndrome Characterized by Renal Disease, Inner Ear Deafness and Ocular Changes, Harefuah **47**:161 (Oct. 15) 1954.

2. Probert, L. A.: Spherophakia with Brachidactyly: Comparison with Marfan's Syndrome, Am. J. Ophth. **36**:1571 (Nov.) 1953.

3. Lloyd, R. I.: A Second Group of Cases of Arachnodactyly, Arch. Ophth. **17**:66 (Jan.) 1937.

4. Marchesani, O.: Brachydaktylie und angeborene Kugellinse als Systemerkrankung, Klin. Monatsbl. Augenh. **103**:392 (Oct.-Nov.) 1939.

5. Bellows, J. G.: Cataract and Anomalies of the Lens, London, Henry Kimpton, 1944, pp. 270-272.

FOLLICULAR LYMPHOMA WITH FULL REMISSION OF LEUKEMIC PHASE

GEORGE J. ANDAY, M.D.
HENRY L. SCHMITZ, M.D.
and
LOUIS R. LIMARZI, M.D., Chicago

TWO OF us (G. J. A. and H. L. S.), in 1952, published a report in the A. M. A. ARCHIVES OF INTERNAL MEDICINE of an unusual case of follicular lymphoma.[1] For a short time this patient had presented the clinical and laboratory findings of acute leukemia, and then these findings had spontaneously disappeared. Repeated lymph node biopsies proved that this patient had follicular lymphoma with sarcomatous changes.

Subsequently we have been searching for the explanation of the peculiar cells ("notched nucleus cells" of Isaacs[2]) which were typically present in the leukemic phase of that case. From a large number of leukemia cases we have studied a few in which "notched nucleus cells" were characteristically present. The results of these studies were briefly presented in the form of a lecture in May, 1953[3]; a more detailed presentation of the subject is now being published elsewhere.[4] The case which is the subject of the present report was chosen from our "notched nucleus cell" material because of certain similarities to the case published in 1952. The present case, as did the previous one, initially presented the clinical and hematological picture of lymphatic leukemia and then spontaneously lost these characteristics. Moreover, lymph node biopsies repeatedly showed the typical picture of follicular lymphoma.

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From the Stritch School of Medicine, Department of Internal Medicine, and Hematology Division, Mercy Hospital, and from the Department of Medicine, University of Illinois College of Medicine and the Research and Educational Hospitals; Associate Clinical Professor of Medicine (Dr. Anday), Clinical Professor of Medicine (Dr. Schmitz), and Associate Professor of Medicine (Dr. Limarzi).

REPORT OF CASE

The patient, a white man, was 68 years of age when first seen, on May 14, 1952.

Present Illness.—He complained of tiredness, shortness of breath, and a sensation of fullness in the abdomen.

Previous History.—The patient stated that his left kidney was removed in 1938 because of a tumor. He recovered satisfactorily from the operation, felt well, and continued to work until December, 1951, when he noticed that his lymph nodes were enlarged. He was seen by his local doctor in December, 1951, and in April, 1952, and was sent to us in May, 1952, for examination and treatment.

Results of Physical Examination.—The patient was very pale. His temperature was 98.4 F. All of the superficial lymph nodes were enlarged. The posterior and anterior lymph nodes of the neck were navy-bean to cherry size. The axillary, inguinal, and femoral nodes were cherry to walnut size. The lips, gums, and soft palate were pale. On examination of the chest a few rales were present at the left base, where the respiratory excursions of the diaphragm were limited. The heart was of normal size. The aortic second sound was accentuated. The blood pressure was 140/80 mm. Hg, and the pulse rate was 118 per minute. The spleen was greatly enlarged; its lower pole could be palpated 10 cm. below the left costal margin. The liver could be palpated 5 cm. below the right costal margin. The extremities and reflexes were normal.

Laboratory Findings.—On the first examination, on May 14, 1952, the red cell count was 3,350,000; the hemoglobin was 10 gm., and the white cell count was 65,000. In the differential count there were 6% segmented cells, 2% band cells, 4% lymphocytes, and 88% "notched nucleus cells." There were 1 or 2 nucleated red blood cells per 100 white blood cells. This and the subsequent blood counts are shown in Figure 1. An iliac puncture performed in May and a sternal puncture in July showed almost complete replacement of the normal bone marrow cells by the "notched nucleus cells" (Table). The platelet count was 120,000. The bleeding, clotting, and clot-retrac-

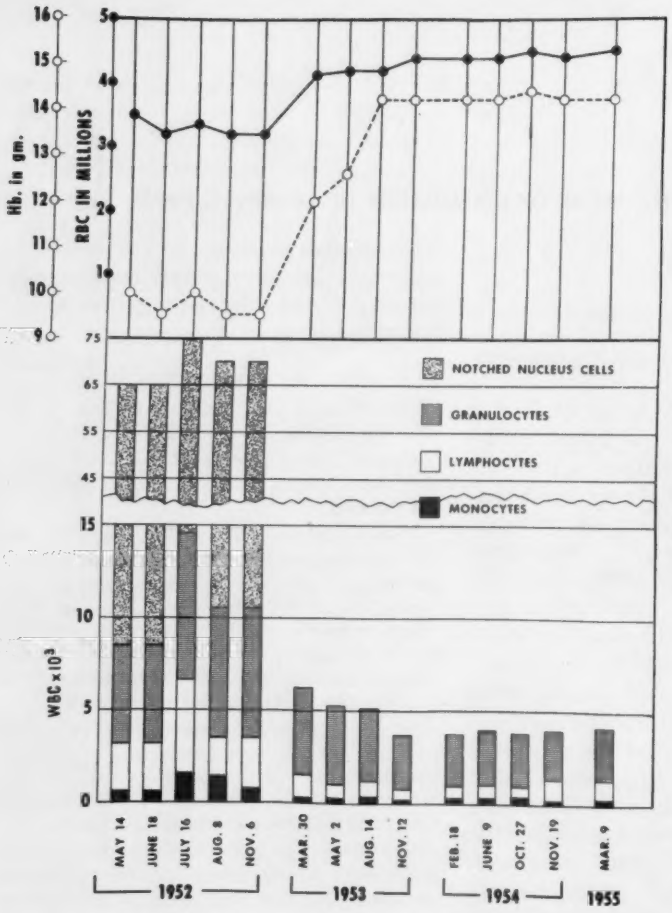


Fig. 1. — Patient's red cell counts and hemoglobin values (top) and the corresponding white cell counts and differential counts (bottom) from May, 1952, to March, 1955. The last blood counts, in September, 1955 (not shown in this chart) were similar to those in March.

Differential Cell Counts in Aspirated Bone Marrow Specimens, from 1952 to 1955

	Differential Count, per Cent				
	6/6/52	7/16/52	3/30/53	10/27/53	3/9/55
Myeloblast	0.1	...	0.2	0.2	0.1
Progranulocyte	0.2	0.3	6.5	8.0	6.0
Myelocyte					
Neutrophile	1.0	1.2	...	...	...
Eosinophile	...	...	6.0	10.0	12.0
Basophile	...	...	1.0	2.0	1.0
Metamyelocyte					
Neutrophile	1.1	1.2	7.0	14.0	12.0
Eosinophile	...	...	1.0	0.5	...
Basophile	...	...	...	...	...
Band cell					
Neutrophile	...	...	6.0	10.0	10.0
Eosinophile	...	...	...	1.0	...
Basophile	...	...	...	...	...
Segmented cell					
Neutrophile	1.0	2.0	10.0	14.0	10.0
Eosinophile	...	...	1.0	1.0	1.0
Basophile	...	...	...	1.0	1.0
Lymphocyte	10.0	16.0	6.0	6.0	5.0
Reticulum cell	0.4	0.1	0.3	0.5	2.0
Plasma cell	...	...	0.4	0.3	0.5
Monocyte	...	...	0.3	0.2	0.5
Megakaryocyte	0.1	0.1	0.1	0.1	0.2
Megakaryoblast	0.1	0.1	0.2	0.2	0.2
Rubriblast	2.0	1.0	4.0	2.0	3.5
Prorubricyte	1.0	2.0	8.0	3.0	4.0
Rubricyte	2.0	2.0	20.0	12.0	14.0
Metarubricyte	2.0	3.0	22.0	14.0	17.0
Notched-nucleus cell	79.0	71.0	...	...	...

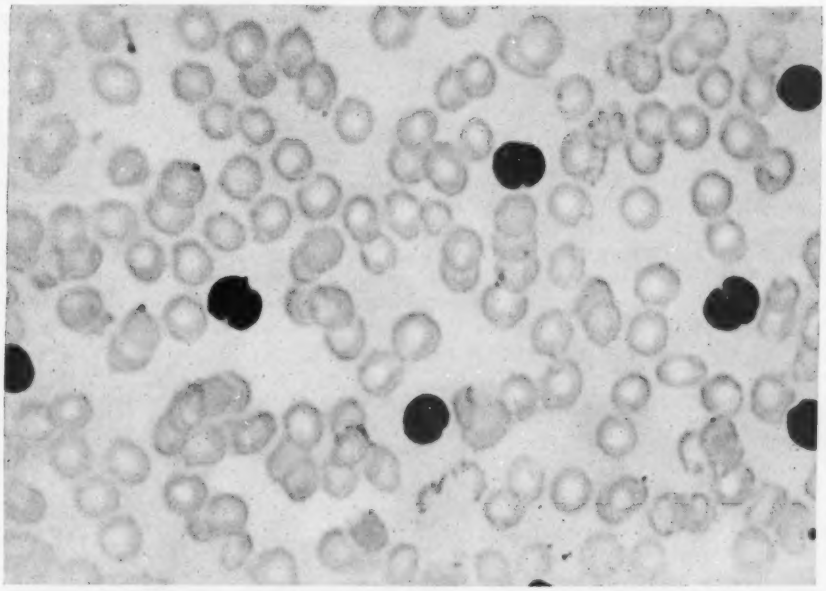
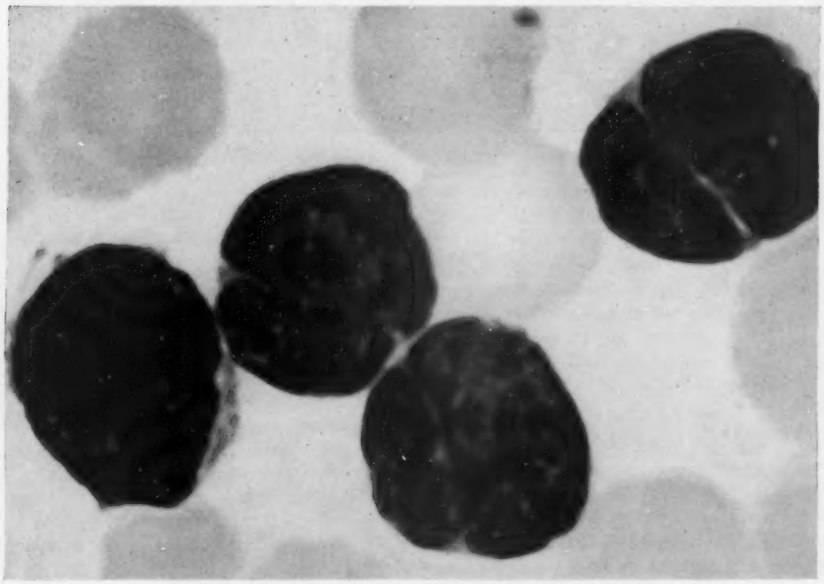


Fig. 2.—Photomicrograph of blood film (May 14, 1952). Notched nucleus cells with two or three notches showed the subsequent cutting of the nucleus into lobes. Wright's stain; × 550.

Fig. 3.—Photomicrograph of blood film (May 14, 1952). Notched nucleus cells. Nuclear details appear with this magnification whereas with lower magnification (Fig. 2) the nuclei appear as silhouettes. Wright's stain; × 1400.



tion time were normal. The Kahn and the heterophile antibody tests were negative. An x-ray picture of the chest showed some tortuosity and calcification of the aorta. The electrocardiogram showed a normal sinus rhythm and left axis deviation. The urinalysis was normal.

At that time, May, 1952, the diagnosis of chronic lymphatic leukemia was supported by the insidious onset, the high white cell count with lymphocytosis, the anemia, and the presence of nucleated red blood cells. Except for the "notched nucleus cells," the bone marrow aspiration biopsies were compatible with lymphatic leukemia. By that time, however, we knew from our study of "notched nucleus cells" that the presence of large numbers of this type of abnormal lymphocyte in the blood was often associated with follicular lymphoma (Figs. 2 and 3). The great enlargement of the spleen made us more suspicious. A supraclavicular lymph node biopsy specimen was examined on July 16, 1952, by Dr. G. A. Bennett. The hematoxylin-and-eosin-stained sections were densely infiltrated with lymphocytes (Fig. 4). In spite of the large numbers of lymphocytes, the follicular structure was outlined. Silver staining for argentophilic fibrils (Gomori's method) showed this follicular structure distinctly (Fig. 5). Some of the cells showed the "notched nucleus." Dr. I. Davidsohn, who reviewed all of these slides, drew our attention to the fact that the walls of the blood vessels, even the smallest ones, were densely infiltrated with the same type of cell.

Subsequent Course.—The patient, a farmer in Michigan about 108 miles from Chicago, came to the city for examination in May, June, July, and August, 1952. He asked us to postpone treatment until late fall. There was no change in his condition on Nov. 30, 1952, when he again refused treatment and hospitalization.

In March, 1953, he came for another examination, at our request. He had apparently gained some weight and had a better color. He stated that he was enjoying better health, was no longer tired or short-winded, and had resumed working on his farm.

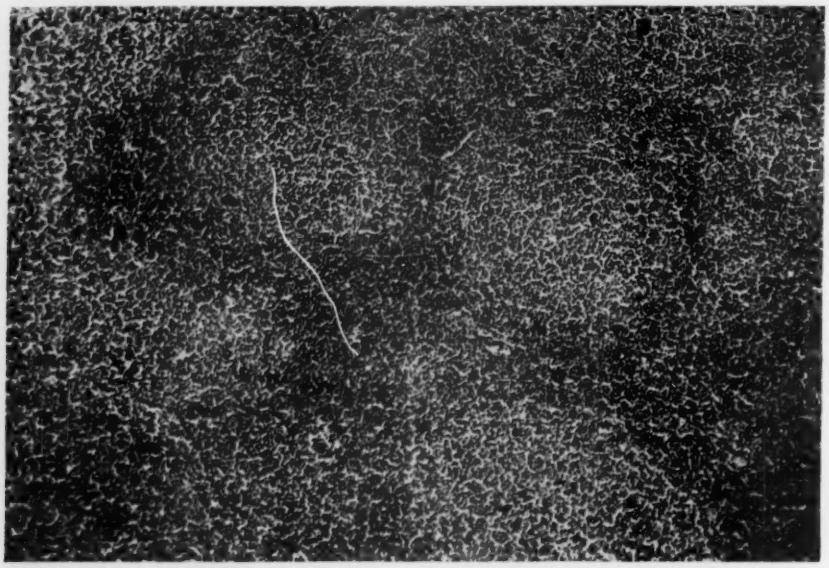


Fig. 4.—Photomicrograph of the first lymph node biopsy specimen (July 16, 1952), when patient was in the leukemic phase. Outlines of the large follicles are indicated through the dense lymphocytic infiltration. Hemotoxylin and eosin; × 90.

On physical examination it was obvious at once that almost all of the superficial lymph nodes had become smaller. Some were not even palpable. The liver was no longer enlarged. The lower pole of the spleen could be felt only on deep inspiration. The laboratory examination revealed 4,140,000 red blood cells, 12 gm. of hemoglobin per 100 cc. of blood, and 6200 white blood cells. The differential count showed 73% segmented cells, 1% band cells, 22% lymphocytes, and 4% monocytes.

Iliac punctures were subsequently performed and showed a normal bone marrow with a mild increase in the red-cell forming elements.

Other lymph node biopsies were performed by Drs. F. Ashley and Robert L. Schmitz in 1953 and

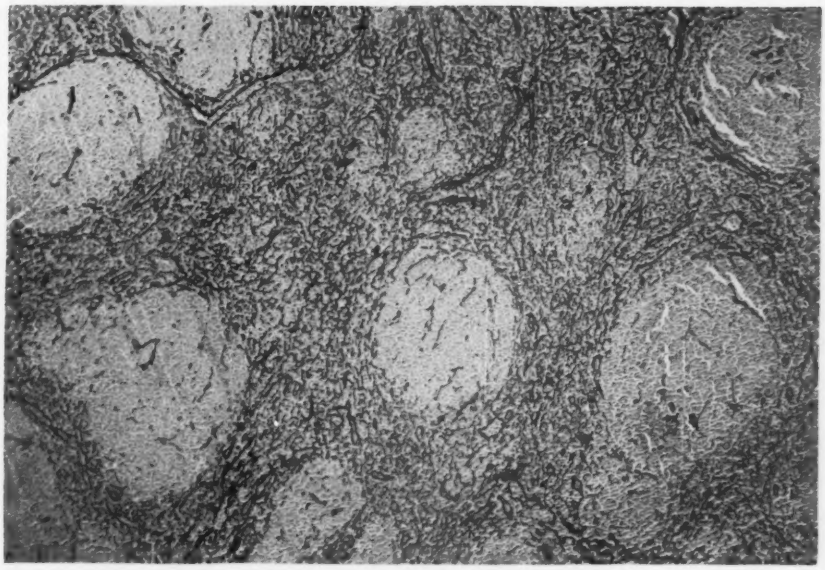
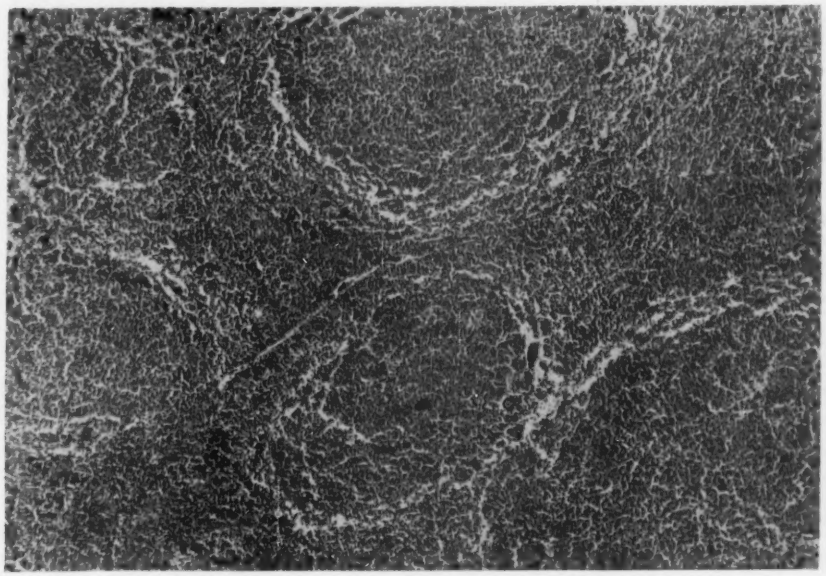


Fig. 5.—Photomicrograph of the same lymph node biopsy specimen (July 16, 1952), stained with Gomori's silver stain; × 63. With this stain the giant follicular structure is conspicuous.

Fig. 6.—Photomicrograph of lymph node biopsy specimen (Nov. 19, 1954). At this time the leukemic features had already disappeared and the patient's blood cell counts were within normal range. The giant follicular structure can be well recognized now, without the superimposed lymphocytic infiltration. Hematoxylin and eosin; × 90.



1954. The sections of these biopsies were examined by Dr. G. G. Brynjolfsson and by Dr. J. H. Peers and now showed the structure of follicular lymphoma without the superimposed leukemic infiltrations (Fig. 6). The cells of the follicles as well as of the interfollicular zones were identical. The argentophilic fibrils in Gomori-stained preparations appeared to be extending into the follicles (Fig. 7). Some of the fibrils were small and broken up. The interfollicular fibrils were densely packed. The blood vessels now were free from infiltrations.

The "notched nucleus cells" have been completely absent from the peripheral blood as well as from the bone marrow since March, 1953. However, these cells could be found in large numbers in the lymph nodes.

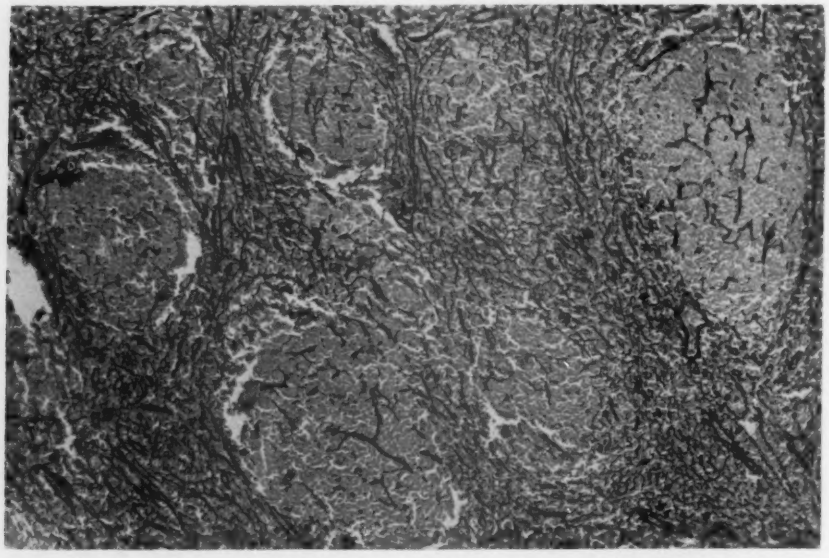


Fig. 7.—Photomicrograph of the same lymph node biopsy specimen (Nov. 19, 1954). Gomori's silver stain; × 63.

The patient, now in his 72d year, is in good general condition and is living a normal life, performing regular daily farm work.

COMMENT

This is the second case in which we have found follicular lymphoma transiently associated with lymphatic leukemia. The first case had the features of an acute leukemia, whereas the second case presented the signs of a chronic leukemia. In the first-reported case no appreciable anemia was observed; in the present case the anemia disappeared when the leukemia spontaneously subsided. The leukemic phase lasted for some weeks in the first case and for somewhat more than a year in the second case. After the leukemia disappeared, both patients developed a mild leucopenia with a mild lymphopenia in the differential count. In the first-reported case the patient had on three occasions at two- to three-year intervals complications due to enlarged lymph nodes. These were relieved by x-ray therapy. In the second case no such complications have occurred. So far, the general condition of these patients is excellent and they are living a normal life with full activity.

The common features in the two cases are the following: (1) the spontaneous disappearance of the leukemia; (2) the underlying giant follicular structure of the lymph nodes; (3) the abnormal, characteristic lymphocyte, the "notched nucleus cell."

1. These two cases of follicular lymphoma apparently are the first on record which showed a spontaneous remission of the associated leukemia. The other leukemic cases of follicular lymphoma reported in the literature * were either constantly associated

* References 5-17 and 23.

with leukemia or terminated with leukemia. Our two cases show that the leukemic features in follicular lymphoma are not inevitably progressive and fatal. They are reversible; the severe clinical and hematological signs and symptoms of leukemia can disappear completely.

In our previous paper [1] we made brief reference to the parallelism in the behavior of the leukemia of lymphosarcoma and that of follicular lymphoma. In the literature, studies based on large numbers of cases offer acceptable evidence that the connection between lymphosarcoma and an associated leukemia is likewise not necessarily a persistent and fatal one. Rather, the connection may be a loose, shifting one. In the same patient leukemic blood features of varying intensity and duration may appear at any stage of the disease.

In our two follicular lymphoma cases the clinical course was remarkably benign as soon as the leukemic features disappeared.

2. Lymph node biopsy was performed during and after the leukemic phase. The basic histological pattern was that of follicular lymphoma. Follicular and interfollicular substances were composed of a single type of cell. During the leukemic phase this pattern had superimposed upon it large numbers of the abnormal lymphocytes. After the leukemic phase only the structure of follicular lymphoma remained.

In this case the "notched nucleus cell" represents an easily recognizable earmark. These cells were present as the leukemic cells in the blood and bone marrow during the leukemic phase. After this phase had cleared, they disappeared from the blood and bone marrow but persisted in the biopsied lymph node. This fact strongly points to the lymph node as their source and port of entry into the circulation.

We wish to emphasize again that "humoral" factors (hormonal or immunological) probably regulate the absence or presence of tumor cells in the circulating blood stream.

3. The "notched nucleus cell" was described by Isaacs [2] in a large number of acute and subacute leukemias. Our subsequent studies [3] indicate that this cell represents a nuclear phenomenon, identical with "amitosis." Such cells have been found in both normal and pathological tissues.

The cells which Ross [18] observed in her cases are probably of this nature. Sherwin and Spirtes [14] found such "amitotic" cells in the blood in a case of follicular lymphoma. Vogel, Erf, and Rosenthal [18] and Vogel and Bassen [19] described a small cell which they called "hematogone." Rosenthal and coworkers [20] described in their cases of follicular lymphoma "the presence of a variable number of unusual lymphocyte-like cells ('hematogones') in the peripheral blood" and also in the bone marrow and lymph node smears. In this later paper [20] the authors added to the earlier description of "hematogones" a new feature that "the nucleus may be partially or completely traversed by a horizontal crack 1 to 2 microns in width, which stains more lightly than the surrounding chromatin." It is obvious from their microphotograms that the cell which they described as a "hematogone" is identical with the "notched nucleus" or "amitotic" cell. In other words, we do not think that this is a different type of cell but rather that it is a lymphocyte which shows the characteristic nuclear patterns of "amitosis," or "notching." Our studies confirm Rosenthal's finding that such cells occur in the blood of normal children.

The nuclear change in "amitosis" is a basic problem of cytology, which is yet unsolved. It is not specific for any given condition. Di Guglielmo † recognizes "amitosis" as one of the earmarks differentiating the leukemic blood picture of lymphosarcoma from lymphatic leukemia. We concur with Rosenthal that its appearance on such large scale in follicular lymphoma is striking.

How frequent is such a mass appearance of "notched nucleus cells" in follicular lymphoma? Is the "notched nucleus cell" the

† References 21 and 22.

cytological counterpart of the histological giant follicular structure? These questions can be answered with statistical data derived from cases in which both histological and cytological studies of the lymph nodes, blood, and bone marrow have been performed.

SUMMARY

The case of a 72-year-old man, suffering from follicular lymphoma, is presented. This patient had the clinical and hematological features of chronic lymphatic leukemia from December, 1951, until November, 1952. Since March, 1953, there have been no signs or symptoms of leukemia. The bone marrow has been normal, with mild normoblastic hyperplasia. Lymph node biopsies performed during the leukemic phase showed the structure of follicular lymphoma with superimposed leukemic infiltration. After the leukemic phase subsided this leukemic infiltration was absent. The characteristic tumor cell in the lymph nodes (as well as in the marrow and blood throughout the leukemic phase) was the "notched nucleus cell." This is the second case we have observed in which the tumor cell leukemia of follicular lymphoma has cleared up completely. Both patients are living and well. The spontaneous termination of the leukemic features seems to point to humoral influences.

REFERENCES

1. Anday, G. J., and Schmitz, H. L.: Follicular Lymphoma with Transient Leukemic Phase, A. M. A. Arch. Int. Med. **89**:621-634 (April) 1952.

2. Isaacs, R.: "Notched Nucleus Cell" Leukemia, Proc. Cent. Soc. Clin. Res. **12**:37 (Oct.) 1939.

3. Anday, G. J.; Limarzi, L. R., and Schmitz, H. L.: "Notched Nucleus Cell" Leukemia, Proc. Inst. Med. Chicago **19**:325-326 (June) 1953.

4. Anday, G. J.; Limarzi, L. R.; Isaacs, R., and Schmitz, H. L.: "Notched Nucleus Cell" Leukemia and the Problem of "Amitosis," to be published.

5. Baehr, G., and Klemperer, P.: Giant Follicle Lymphoma, New York J. Med. **40**:7-11 (Jan. 1) 1940.

6. Symmers, D.: Giant Follicular Lymphadenopathy With or Without Splenomegaly, Arch. Path. **26**:603-647 (Sept.) 1938.

7. Uhlmann, E. M.: The Significance of Giant Follicular Lymphadenopathy, Radiology **50**:147-156 (Feb.) 1948.

8. Saxén, E.: On Giant Follicular Lymphadenopathy, Acta path. et. microbiol. scandinav. **26**: 840-854, 1949.

9. Ehrlich, J. C., in discussion on Cohen, S. E., and Bergstrom, V. W.: Giant Follicle Lymphadenopathy, New York J. Med. **49**:273-278 (Feb. 1) 1949.

10. Custer, R. P., and Bernhard, W. G.: The Interrelationship of Hodgkin's Disease and Other Lymphatic Tumors, Am. J. M. Sc. **216**:625-642 (Dec.) 1948.

11. Gall, E. A.; Morrison, H. R., and Scott, A. T.: The Follicular Type of Malignant Lymphoma: A Survey of 63 Cases, Ann. Int. Med. **14**:2073-2090 (May) 1941.

12. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathologic Survey of 618 Cases, Am. J. Path. **18**:381-415 (May) 1942.

13. Ross, J. M.: The Pathology of the Reticular Tissue Illustrated by 2 Cases of Reticulosis with Splenomegaly and a Case of Lymphadenoma, J. Path. & Bact. **37**:311-329, 1933.

14. Sherwin, B., and Spirtes, M.: Follicular Lymphoblastoma, Ann. Surg. **111**:459-469 (March) 1940.

15. Germini, P., and Dotta, F.: Su di un caso di linfopatia cronica splenomegalic (morbo di Brill-Symmers?) terminante in leucemia acute a decorso polifasico, Progr. med. Napoli **10**:391-396 (July 15) 1954.

16. Dancsházy, M., and Herendi, V.: A Makrofolliculáris Lymphoblastomáról, Orvosi hetil. **93**: 675-676 (June 8) 1952.

17. Ikeda, K.: Follicular Splenomegaly Brill's Type? Arch. Path. **1**:658-661 (April) 1926.

18. Vogel, P.; Erf, L. A., and Rosenthal, N.: Hematological Observations on Bone Marrow Obtained by Sternal Puncture, Am. J. Clin. Path. **7**: 436-447 (Sept.); 498-515 (Nov.) 1937.

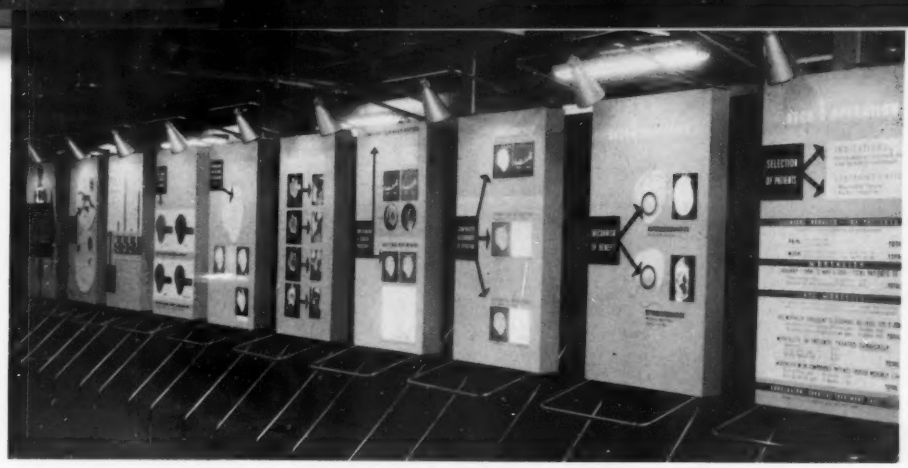
19. Vogel, P., and Bassen, F. A.: Sternal Marrow of Children in Normal and in Pathologic States, Am. J. Dis. Child. **57**:245-268 (Feb.) 1939.

20. Rosenthal, N.; Dreskin, O. H.; Vural, I. L., and Zak, F. G.: The Significance of Hematogones in Blood, Bone Marrow and Lymph Node Aspiration in Giant Follicular Lymphoblastoma, Acta haemat. **8**:368-377 (Dec.) 1952, p. 369.

21. Di Guglielmo, G.: Rapporti tra il linfosarcoma e la leucemia linfatica, Progr. med. Napoli **9**:489-494 (Aug. 31) 1953.

22. Di Guglielmo, G.: Rapporti tra il linfosarcoma e la leucemia linfatica, Sangue **26**:244-258, 1953.

23. Wieme, R. J.: Een geval van ziekte van Brill-Symmers (lymphoma gigantum folliculare) met leukotische reactie en normal proteinogram, Belg. tijdschr. geneesk. **10**:1166-1169 (Dec. 15) 1954.



Scientific Exhibits

OPERATIONS FOR CORONARY ARTERY DISEASE

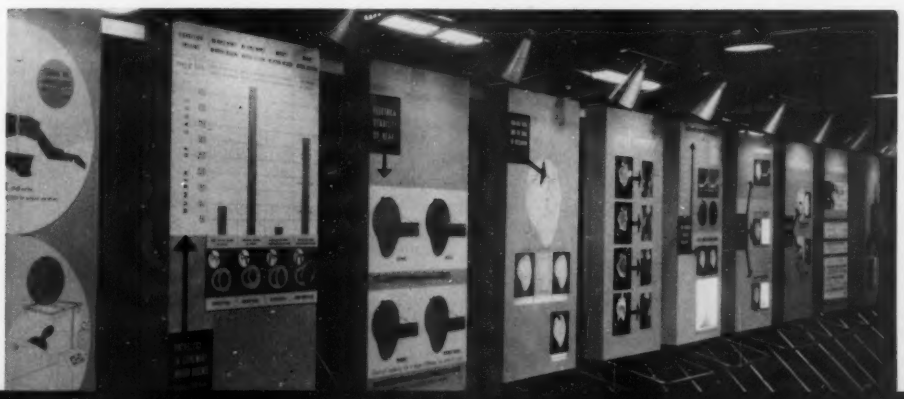
CLAUDE S. BECK, M.D. and DAVID S. LEIGHNINGER, M.D.
Cleveland

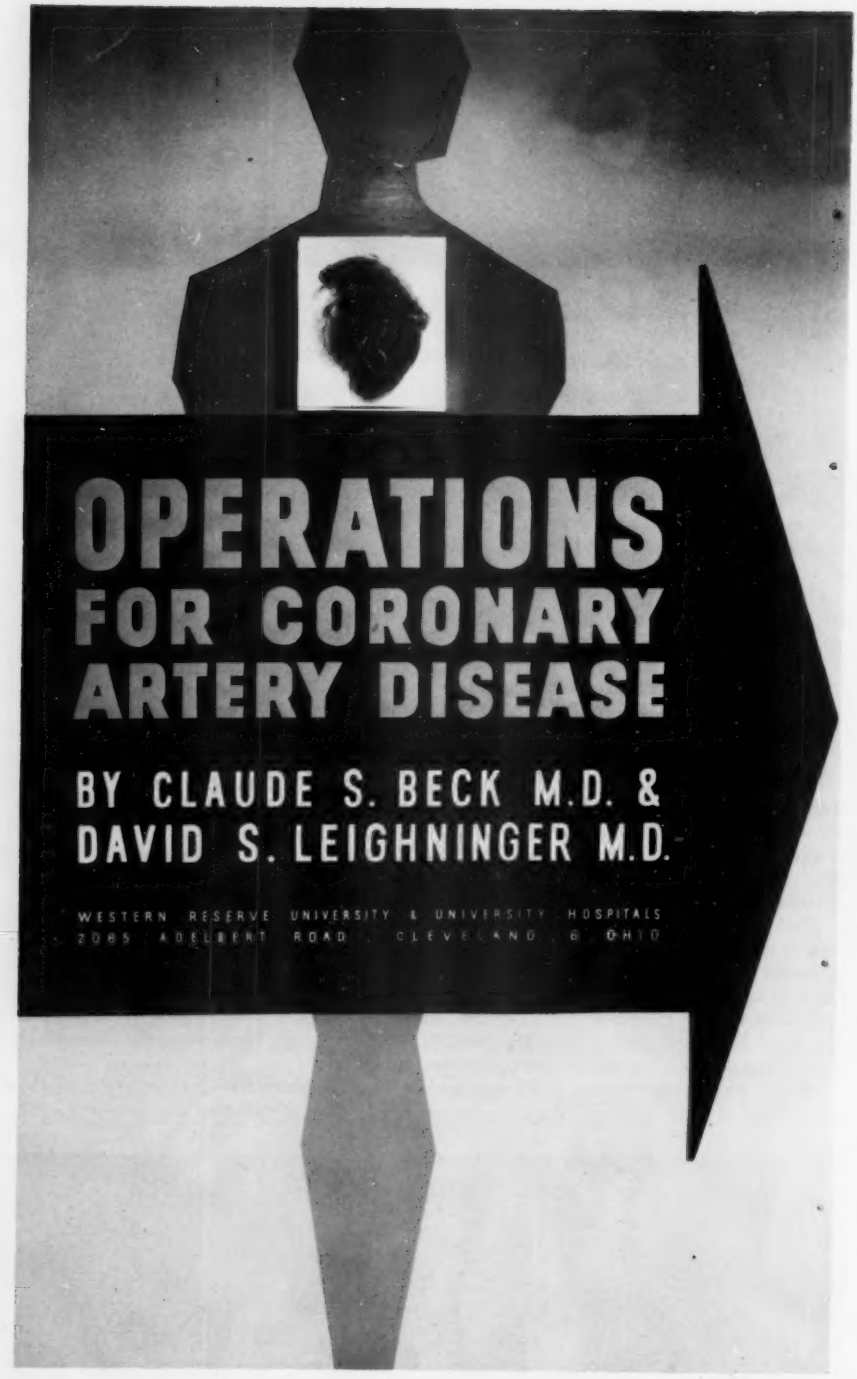
This exhibit is based upon facts obtained in the research laboratory where the coronary blood vessels were dealt with directly. This direct approach has yielded information that could not be obtained in any other way. The facts thus established are new and different, and up to the present time they have received little or no attention from the medical cardiologist. If the treatment of coronary disease is going to improve, it must first change. It cannot improve if it remains static. Information presented here calls for changes in treatment, and it is our duty to decide what these changes should be.

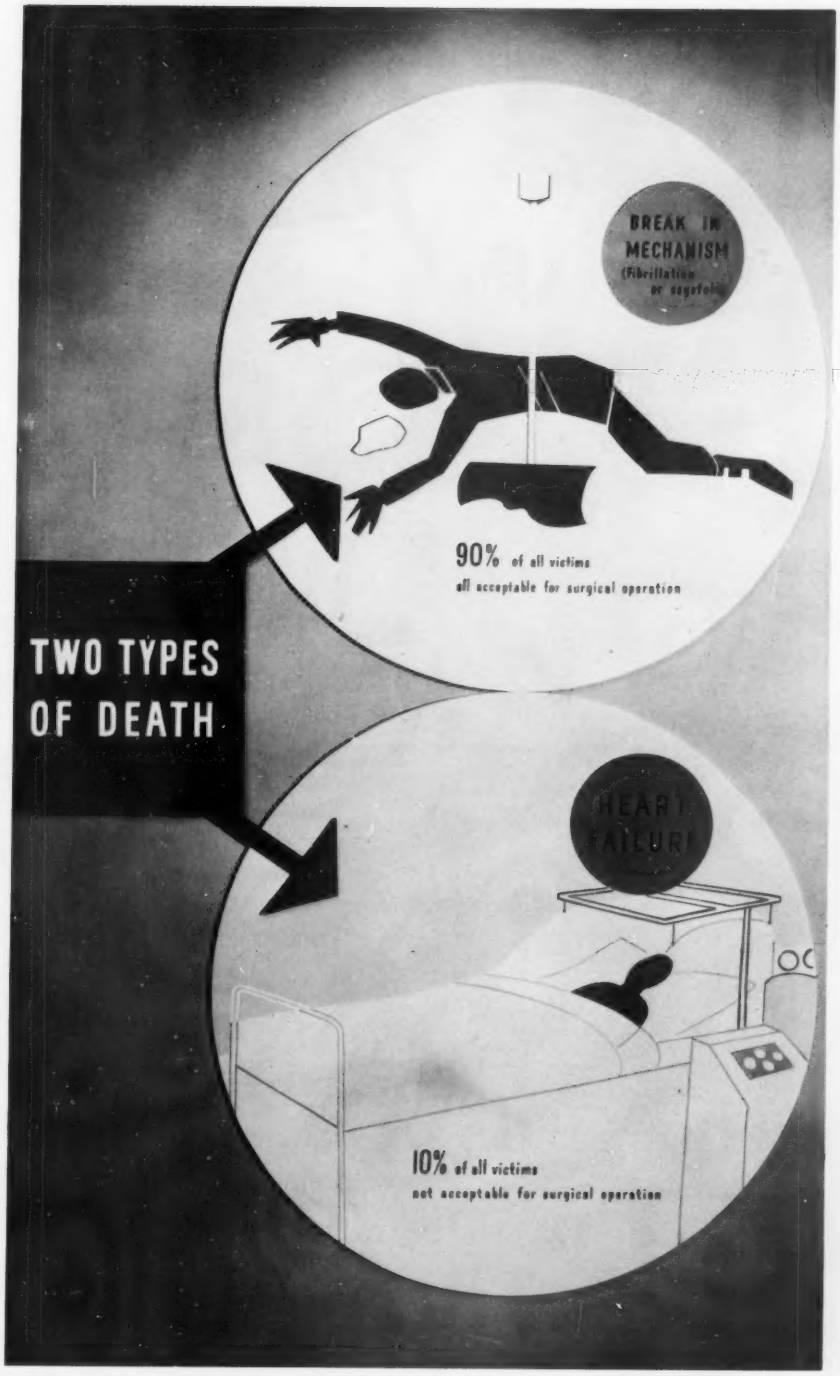
One of the facts established experimentally concerns the distribution of oxygen to various parts of the heart muscle. An electrical tracing taken from a uniformly cyanosed heart is the same as the tracing taken from a uniformly well oxygenated heart. Each of these hearts is electrically stable. When the cyanosed heart stops beating, it goes into asystole; it does not fibrillate. Each heart becomes electrically unstable when the distribution of oxygen is not uniform. A well oxygenated heart becomes unstable when an area of muscle is deprived of blood, and a cyanosed heart becomes unstable when an area is perfused with arterial blood. The term "oxygen differential" is applied to these conditions, and this differential is related to the production of electrical currents which may be strong enough to fibrillate the heart. The problem in coronary artery disease, therefore, is not entirely one of total inflow into the arteries, but in most patients it is a matter of distribution of the blood that enters these arteries. An arterial occlusion can destroy muscle without producing fatal currents, and, vice versa, fatal currents may appear without producing infarction. There are two types of death in coronary artery disease. In one type the coordinated mechanism is destroyed; in the other the mechanism is not destroyed but the myocardium is destroyed and heart failure develops.

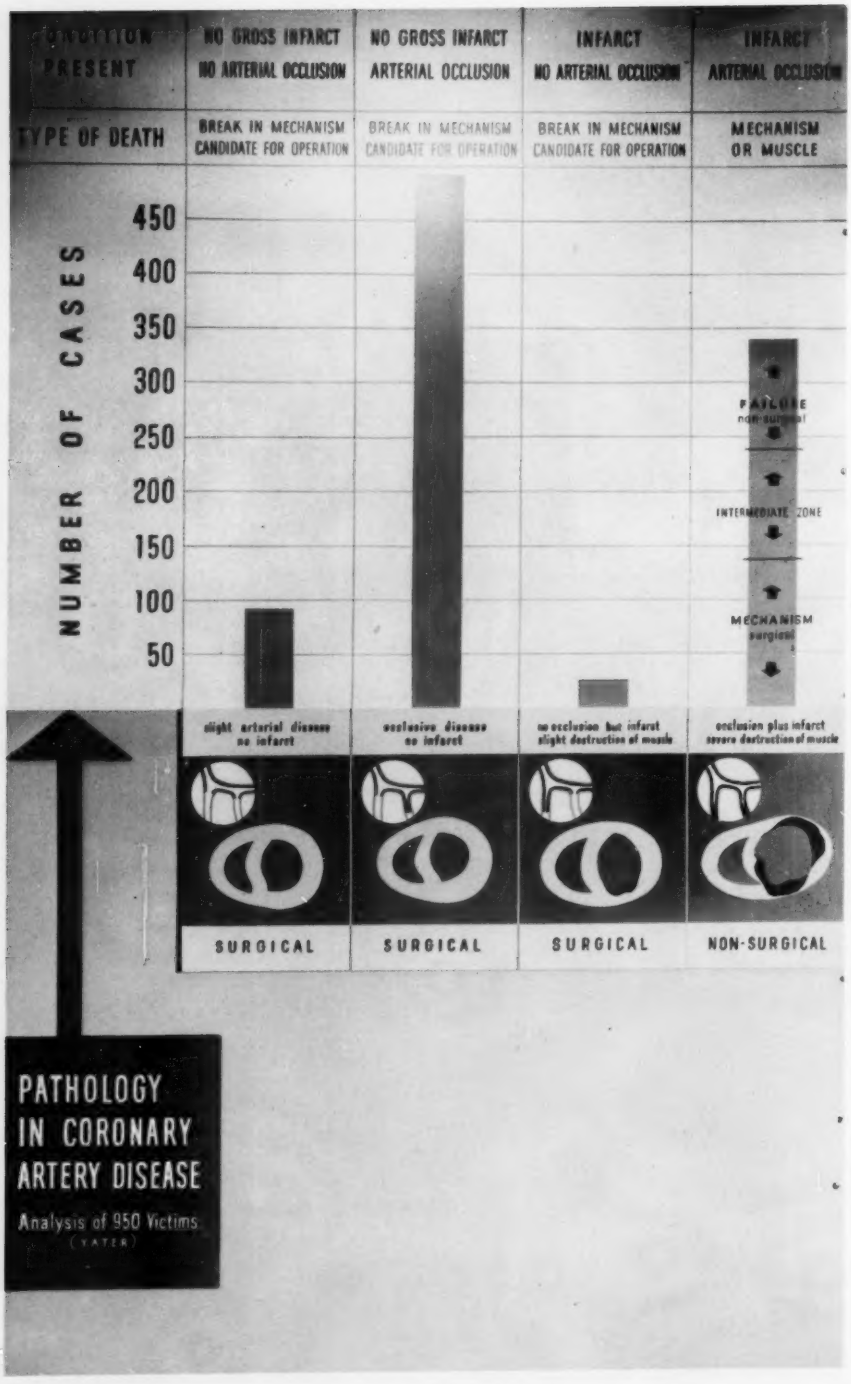
Oxygen differentials and electrical potentials are reduced by making more blood available to ischemic muscle. Operation if done before an artery is occluded accomplishes this. When the circumflex artery is ligated at its origin, there is an average of 228 cc. of blood available per hour to the muscle distal to the ligature. After operation this figure rises to 510. Thus the operation perfuses 282 cc. per hour in addition to the blood that is already there. This blood is there to meet the crisis of occlusion. A total of 300 cc. per hour reduces the electrical potentials to safe levels when the descending artery is ligated, and 390 cc. does this for the circumflex artery.

Results obtained on patients fulfill expectations from the laboratory. It is necessary for the internist to see these patients to appreciate the amount of benefit from operation.

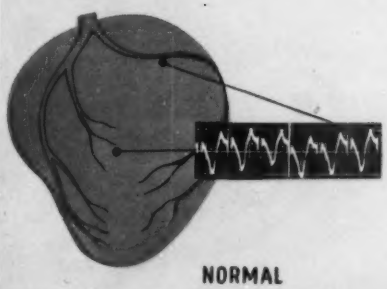



OPERATIONS
FOR CORONARY
ARTERY DISEASE
BY CLAUDE S. BECK M.D. &
DAVID S. LEIGHNINGER M.D.
WESTERN RESERVE UNIVERSITY & UNIVERSITY HOSPITALS
2085 ADELBERT ROAD CLEVELAND 6 OHIO

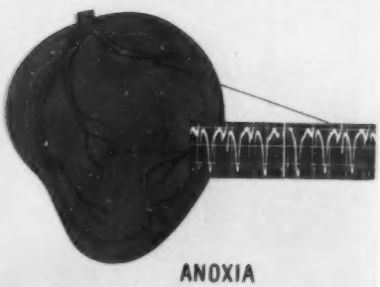

BREAK IN MECHANISM
(Fibrillation or asystole)
90% of all victims
all acceptable for surgical operation
TWO TYPES OF DEATH
HEART FAILURE
10% of all victims
not acceptable for surgical operation


CONDITION PRESENT
NO GROSS INFARCT NO ARTERIAL OCCLUSION
NO GROSS INFARCT ARTERIAL OCCLUSION
INFARCT NO ARTERIAL OCCLUSION
INFARCT ARTERIAL OCCLUSION
TYPE OF DEATH
BREAK IN MECHANISM CANDIDATE FOR OPERATION
BREAK IN MECHANISM CANDIDATE FOR OPERATION
BREAK IN MECHANISM CANDIDATE FOR OPERATION
MECHANISM OR MUSCLE
NUMBER OF CASES
450
400
350
300
250
200
150
100
50
FAILURE non-surgical
INTERMEDIATE ZONE
MECHANISM surgical
slight arterial disease no infarct
occlusive disease no infarct
no occlusion but infarct slight destruction of muscle
occlusion plus infarct severe destruction of muscle
SURGICAL
SURGICAL
SURGICAL
NON-SURGICAL
PATHOLOGY IN CORONARY ARTERY DISEASE
Analysis of 950 Victims
(YATER)

ELECTRICAL STABILITY OF HEART

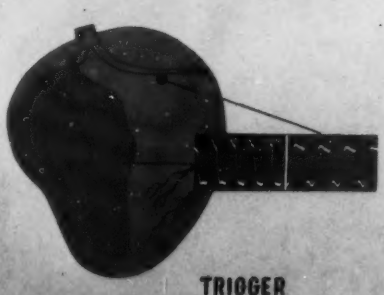


NORMAL

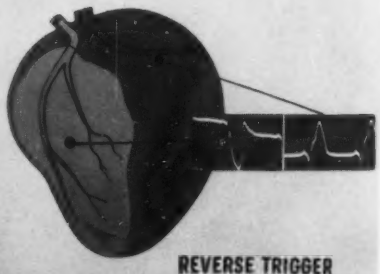


ANOXIA

EACH ELECTRICALLY STABLE - DOES NOT FIBRILLATE



TRIGGER

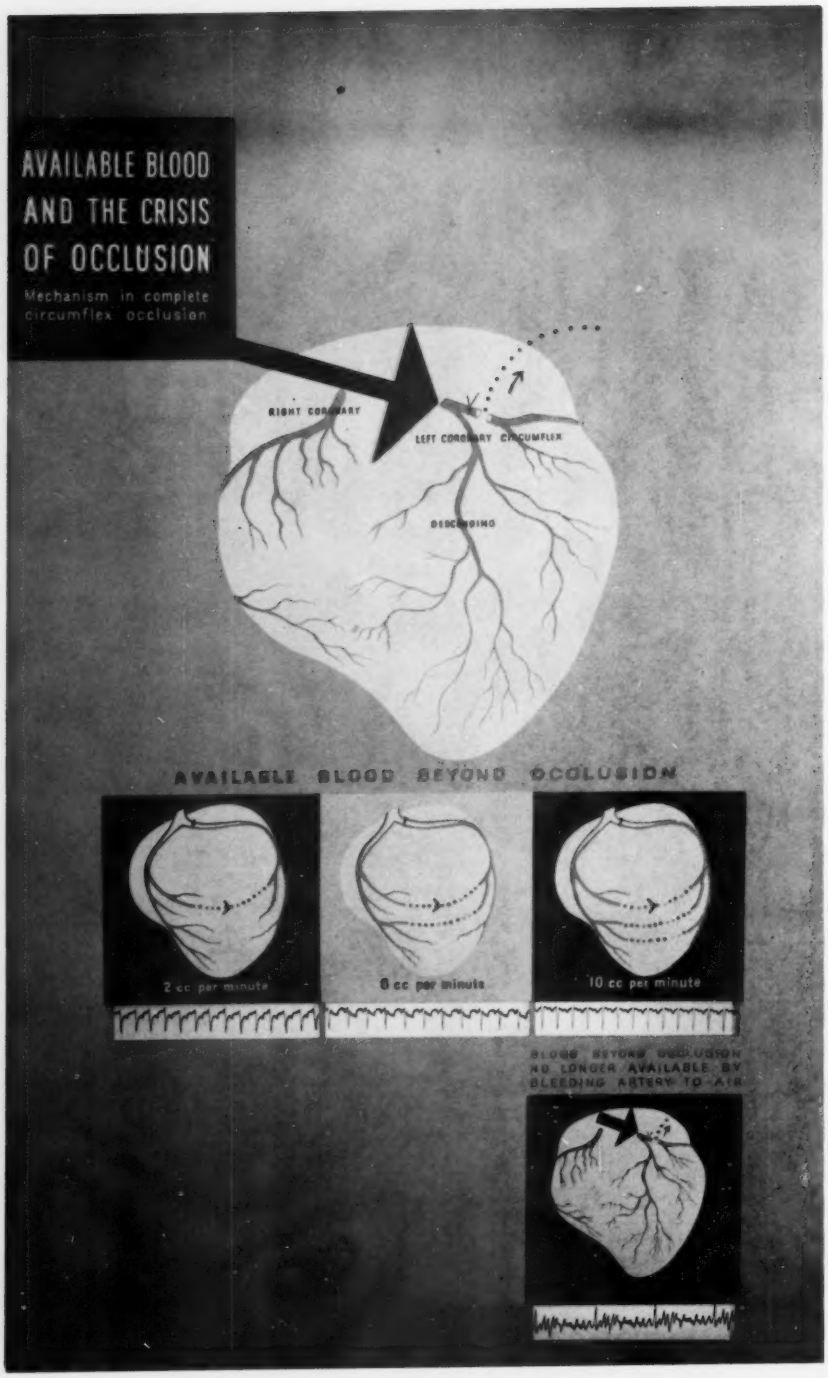


REVERSE TRIGGER

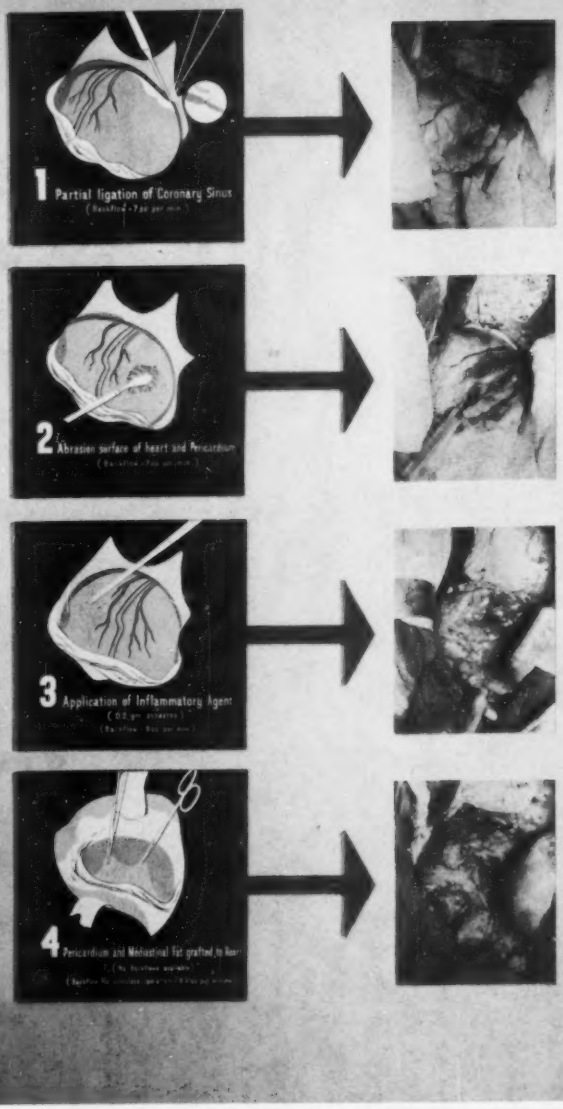
Electrical instability due to oxygen differential - "not current of injury"

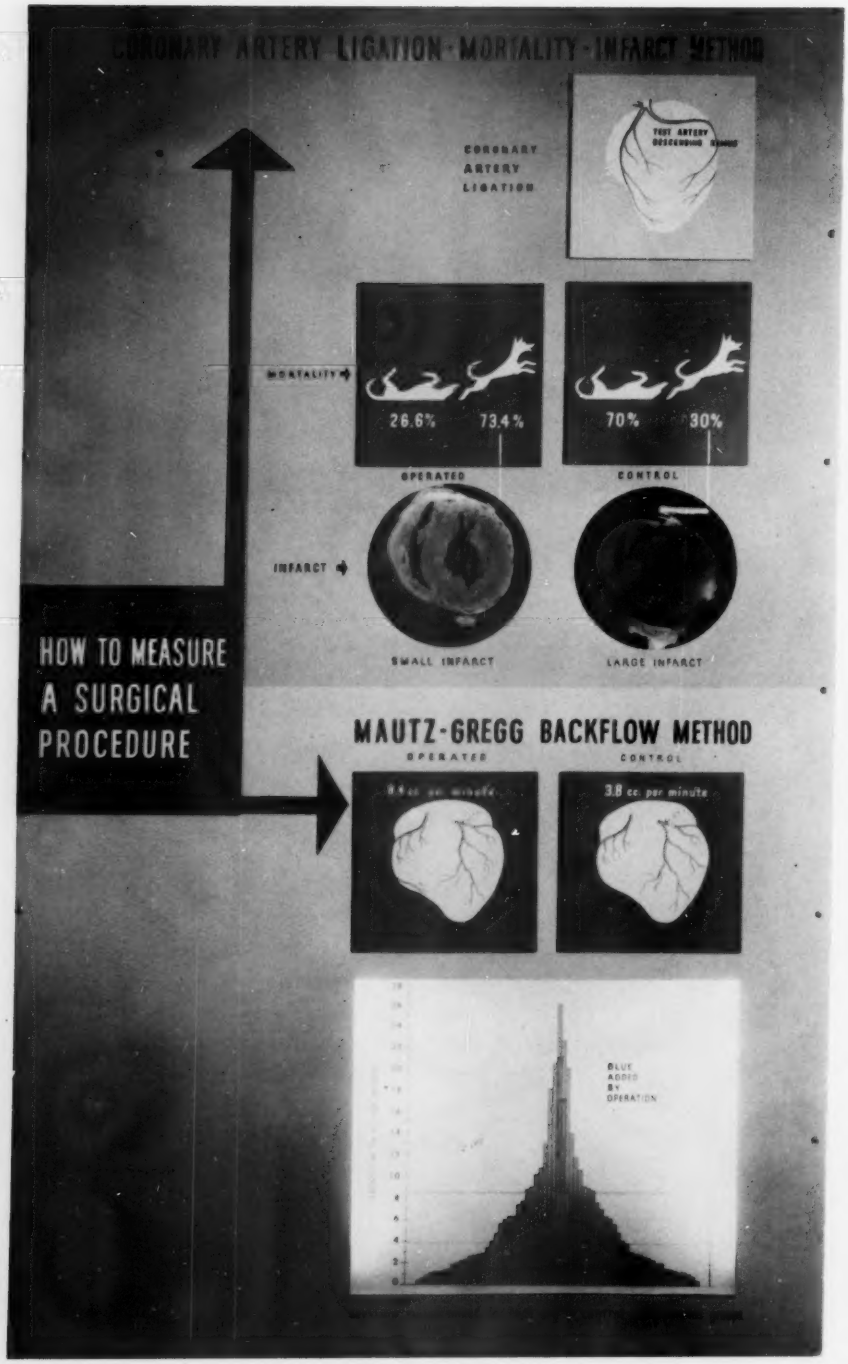
EACH ELECTRICALLY UNSTABLE → VENTRICULAR FIBRILLATION → DEATH

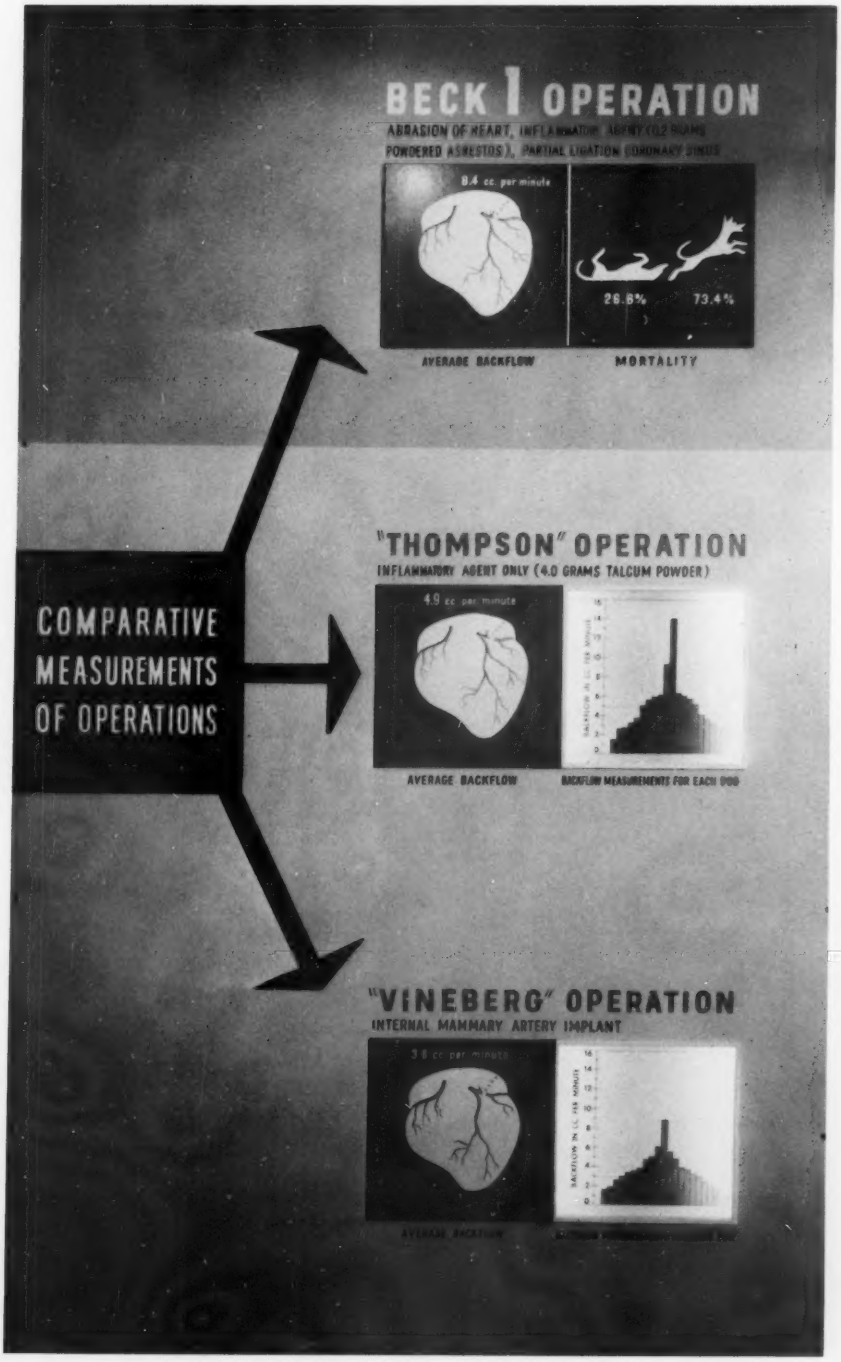
One third of all victims die of this instability without infarction


AVAILABLE BLOOD AND THE CRISIS OF OCCLUSION
Mechanism in complete circumflex occlusion
RIGHT CORONARY
LEFT CORONARY CIRCUMFLEX
DESCENDING
AVAILABLE BLOOD BEYOND OCCLUSION
2 cc per minute
6 cc per minute
10 cc per minute
BLOOD BEYOND OCCLUSION NO LONGER AVAILABLE BY BLEEDING ARTERY TO AIR

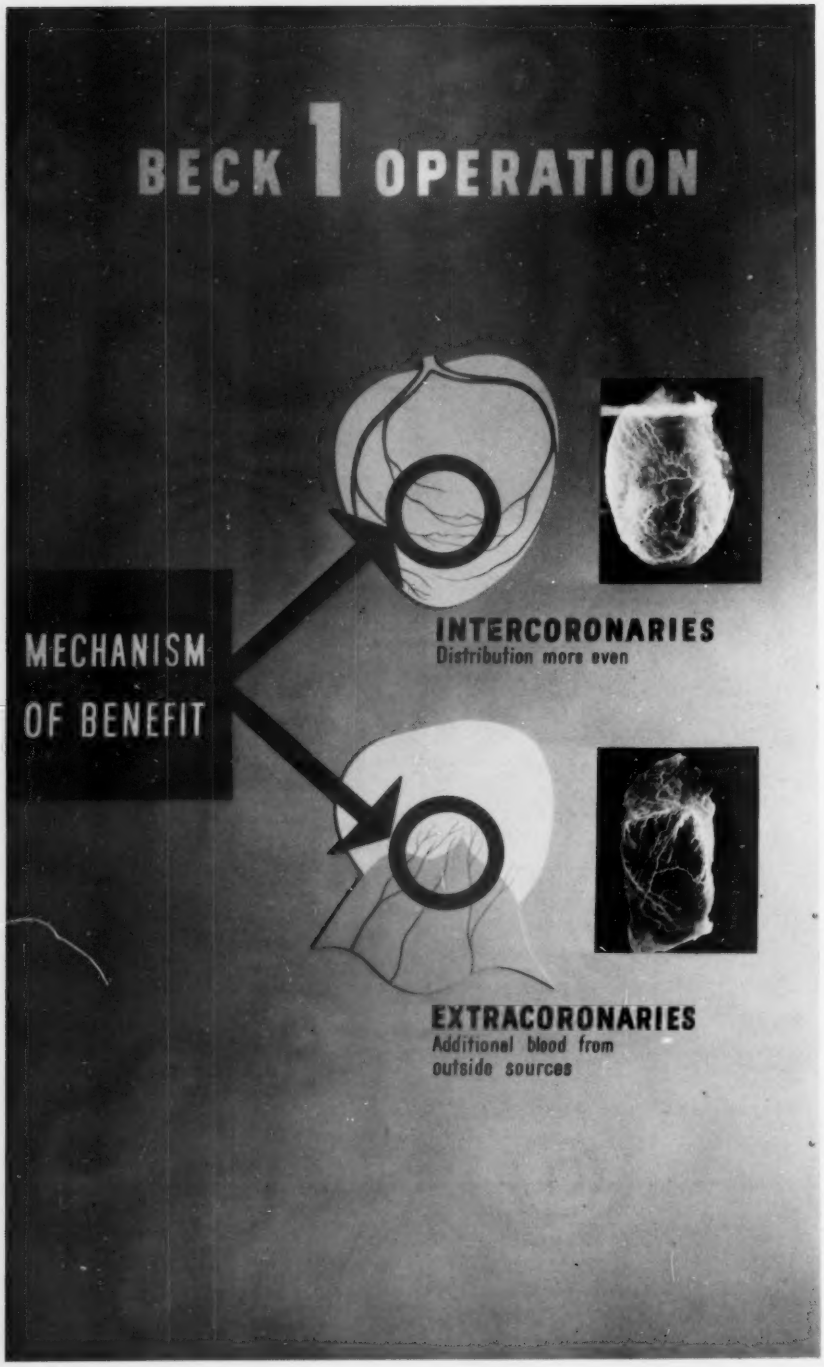
BECK 1 OPERATION


1 Partial ligation of Coronary Sinus
2 Abrasion surface of heart and Pericardium
3 Application of Inflammatory Agent
4 Pericardium and Mediastinal fat grafted to heart


CORONARY ARTERY LIGATION - MORTALITY - INFARCT METHOD
CORONARY ARTERY LIGATION
MORTALITY
26.6%
73.4%
OPERATED
70%
30%
CONTROL
INFARCT
SMALL INFARCT
LARGE INFARCT
HOW TO MEASURE A SURGICAL PROCEDURE
MAUTZ-GREGG BACKFLOW METHOD
OPERATED
CONTROL
3.8 cc. per minute
BLUE ADDED BY OPERATION


BECK 1 OPERATION
ABRASION OF HEART, INFLAMMATORY AGENT (0.2 GRAMS POWDERED ASBESTOS), PARTIAL LIGATION CORONARY SINUS
8.4 cc. per minute
26.8%
73.4%
AVERAGE BACKFLOW
MORTALITY
COMPARATIVE MEASUREMENTS OF OPERATIONS
"THOMPSON" OPERATION
INFLAMMATORY AGENT ONLY (4.0 GRAMS TALCUM POWDER)
4.9 cc. per minute
AVERAGE BACKFLOW
BACKFLOW MEASUREMENTS FOR EACH DOG
"VINEBERG" OPERATION
INTERNAL MAMMARY ARTERY IMPLANT
3.8 cc. per minute

BECK 1 OPERATION



BECK 1 OPERATION

SELECTION OF PATIENTS

INDICATIONS

Positive diagnosis of coronary disease made by medical cardiologist

CONTRAINDICATIONS

1. Myocardial Failure
2. Recent infarction

CLINICAL RESULTS - 103 PATIENTS

6 months or more postoperative, who could be evaluated

PAIN — NO PAIN 45%; LESS PAIN 45% — **TOTAL 90%**

WORK — BETTER ABLE TO WORK, NO LIMITATIONS 35%; BETTER ABLE TO WORK, SOME LIMITATIONS 55% — **TOTAL 90%**

MORTALITY

JANUARY 1, 1954 TO MAY 6, 1955 - TOTAL PATIENTS 75

Thoracotomy alone — 2 patients - 2.6%
Operative and early postoperative - 3 patients - 4.0%
(From discharge up to 15 months - 2 patients - 2.6%)

TOTAL 6.6%

LATE MORTALITY

That operation saves life after coronary occlusion is proven experimentally. It is difficult to prove this on patients but a favorable trend has been established.

LATE MORTALITY, SUBSEQUENT TO DISCHARGE, ALL CASES, 1935 TO JUNE, 1954

136 patients - from discharge up to one year - 9 deaths - 6.6%
83 patients - from one year up to two years - 4 deaths - 4.8%

TOTAL 11.4%

MORTALITY IN PATIENTS TREATED SURGICALLY

Operative 6.6%
During first year 6.6%
During second year 4.8%

TOTAL 18.0%

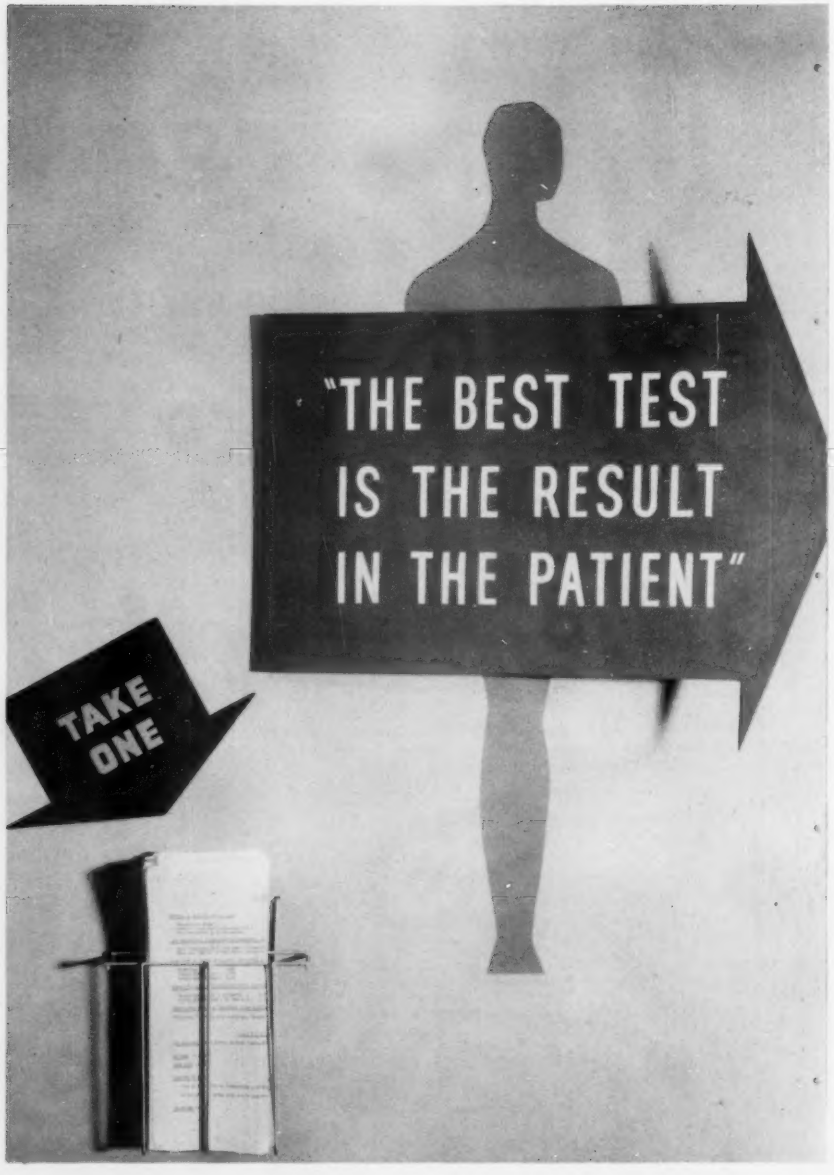
MORTALITY IN 88 COMPARABLE PATIENTS TREATED MEDICALLY (Lindgren*)

During first year — 15 deaths - 17%
During second year - 11 deaths - 13%

TOTAL 30%

CONCLUSION: SURGICAL TREATMENT SAVES LIVES

* Lindgren, I.: Acta med. scandinav. (supp. 243) 136:1, 1950.



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Western Reserve University and University Hospitals.

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Shown as a scientific exhibit of the Section on Surgery, General and Abdominal, at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955.

This exhibit was paid for in part by Thompson Products, Inc., Cleveland. The experimental work was supported by the U. S. Public Health Service and the Cleveland Area Heart Society.

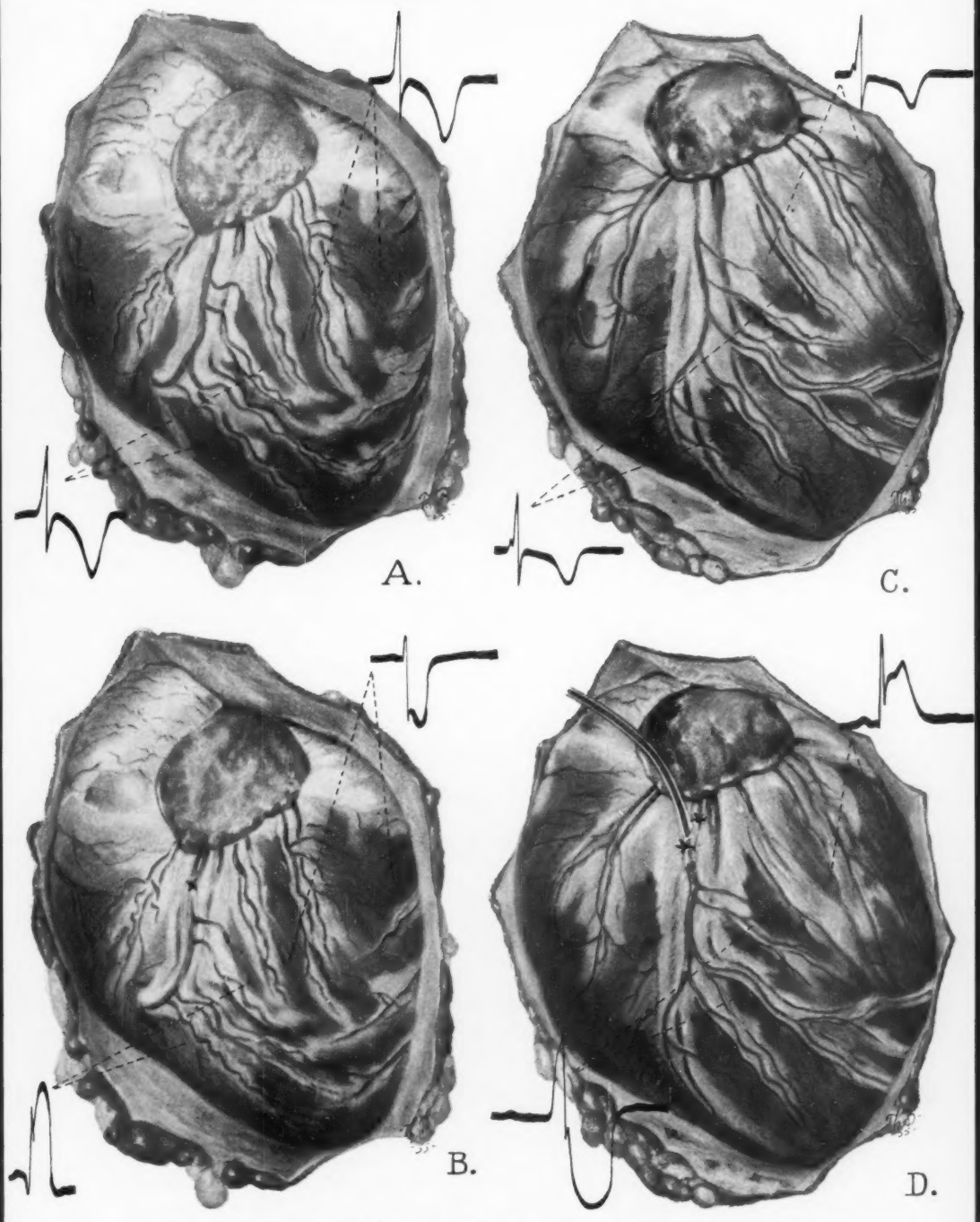

Fig. 2.—Dog hearts illustrating four conditions of myocardial oxygenation, with direct epicardial electrocardiograms demonstrating measurement of electrical potentials. *A* and *C* are the same heart; the one is uniformly well oxygenated, and the other is uniformly and severely cyanosed. These hearts are electrically stable as shown by the isoelectric S-T segment in each condition. *B* and *D* are electrically unstable because the oxygen tension in each heart is not uniform throughout. The S-T segment is depressed over the pink or well-oxygenated myocardium and elevated over the blue or cyanosed myocardium. These differences in potentials are often strong enough to fibrillate the heart. The term "current of oxygen-differentials" is introduced to replace "current of injury," which is obviously incorrect. A uniformly cyanosed heart is not an injured heart.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

First International Conference on Thrombosis and Embolism. By T. H. Koller and W. R. Merz. Price, 76 Fr. (Swiss). Pp. 1316. Benno Schwabe & Co., Basel 10, 1955.

This collection of papers, presented at the First International Conference on Thrombosis and Embolism, brings together opinions and thoughts of outstanding authorities in the field of thromboembolic disease. The papers have been arranged systematically into groups dealing with each phase of the subject. The articles are about equally divided among the English, German, and French languages. Short summaries in each language are provided at the conclusion of every paper. Excellent bibliographies are provided with the individual papers.

The section on anticoagulant therapy with various heparinoid and coumarin compounds should be of particular interest to internists. The papers evaluating efficacy of tests used to control anticoagulant dosage should also prove of value to clinicians using these drugs.

The combination of a comprehensive review of basic research in this field plus methods and statistics of clinicians experienced in both thromboembolic and hemorrhagic disease makes this volume a good reference for internists, surgeons, pathologists, and physiologists with interest in this subject.

WILLIAM P. JOLLY, M.D.

Josiah Macy, Jr. Foundation 1930-1955 and Second Report of the Helen Hay Whitney Foundation, 1950-1954. Pp. 174.

Reviewing reports of foundations generally is not a useful exercise for physicians. These two reports, neatly bound and shrewdly edited, serve as a taking-off point for a consideration of the role which foundations have played and which they might play, not only in American medicine but in the broad field of education and in the affairs of the world at large. There is scarcely any endeavor which may not be forwarded by a foundation. There is no objective for which one cannot bequeath large or small sums. No one has ever calculated the vast sums of money wasted by devoted but misguided zealots bemused by some enthusiastic promoter or tormented by some pathological whim. Such travesties on altruism may be seen particularly where large quantities of wealth accumulate in a short period of time. For reasons not apparent, many established whimsies have been supported by fortunes made by exploitation of natural resources such as oil, mining, and the destruction of forests. Many foundations, however, serve very useful purposes. A study has never been made of the influence which has resulted and still comes from the massive benefactions of Rockefeller, Carnegie, and Ford. There is hazard in whether or not the bounty of those who have accumulated wealth and who have altruistic motives will accomplish good, be wasted, or produce positive harm. By the very nature of foundations and the people who manage them, there is a tendency for conservatism of opinion, lag in communication, and a general resistance to anything which changes the administrators' quiet way of life.

Medical foundations as a rule have as their directors persons who have been productive in medicine either in teaching or in investigation. But the mere fact that they accept responsibility for directing a foundation suggests that they find their productivity arriving at a natural end. If it is not they may bring it to an end by taking over administrative duties. Their view of medicine and research, despite the best intentions and the greatest wisdom, tends to be detached more and more from the active probing points where knowledge confronts ignorance. For administrative ease there is a trend to attack segments of the disease. Many series of projects breed reports which can be swelled out with references to many advances and to much published work. A question which well might be asked is this: "Is it not time to have some council of wise men, well known to the community at large, of whom advice could be sought about what fields are most in need of research and where research is most likely to be productive—productive not so much in application as in new ideas."

These questions are no indication that the Helen Hay Whitney Foundation or the Josiah Macy, Jr., Foundation have been anything but models in their aims and achievements. The Helen

Hay Whitney Foundation has as its goal finding out more about the cause of rheumatic fever and rheumatic heart disease and if they may be reduced as important dangers. In this area, advance has been slow, though steady and sound. We have not encountered the breathless announcement via mass media that a cure is around the corner if not already here. To perhaps a unique degree, this Foundation's accomplishments may be looked upon as a memorial to Dr. Duckett Jones, who personified the spirit of the organization and gave it wise direction. It is to be hoped that his too early death does not dislocate its program.

Probably the most notable achievements of the Josiah Macy Foundation are the establishment of their conference programs. The proceedings of many of them have been reviewed in these columns: Their philosophy in education emphasizes a sound approach to patients without letting emphasis on psychosomatic medicine raise up another medical religion or subspecialty. Also, many of us have the most happy recollection of receiving numerous medical reprints during activities in World War II, a very wise and thoughtful benefaction which certainly encouraged many physicians to keep up with current medicine under the least auspicious circumstances.

A great risk of all foundations with exclusive and special programs is that they tend to become rigid, their conservatism gets wasteful, their overhead may perpetuate too large a staff of administrators, and they may fail to recognize the opportunity to advance science, education, and welfare because they restrict their efforts to one disease or fraction therof. These progress reports demonstrate that the Whitney and Macy foundations have escaped this danger so far. If this is more than good fortune we should learn the reasons, that they may form thoughtful policy rather than depend on chance.

WILLIAM B. BEAN, M.D.

The Teaching of Pathology, Microbiology, Immunology, and Genetics: Report of the Second Teaching Institute of the Association of American Medical Colleges, French Lick, Oct. 10-15, 1954. Compiled by the Committee on the 1954 Teaching Institute. Association of American Medical Colleges, 185 N. Wabash Ave., Chicago 1; *J. M. Education* **30**:1-164 (Sept., Pt. 2) 1955.

The period since World War II has seen a great upsurge in a formal and organized approach to problems of medical education. Part of this is a natural outgrowth of the developments which have revolutionized medical education in its entirety. We tend to look on contemporary medical education as a development of the contributions of Johns Hopkins Hospital and Harvard Medical School supplemented and indeed deflected by the Flexner report. But things are more complex, and now we are caught up in all the multitudinous new advances which have stuffed the curriculum to bursting. The sometimes self-conscious introspections of medical teachers are made fretful by Education and all the machinery of examinations, committee evaluations, student opinion polls, and the like. The story of the influence of the great Eastern universities and medical schools has been told and many times over. No one has traced out the conspicuous influence of midwestern universities. For example, the University of Michigan contributed Mall, Abel, Howell, Hurd to the Johns Hopkins Medical School. The scope of American medicine has passed far beyond the leadership of one or even a few schools. This is seen in the revival of self critique among physicians.

This symposium or gigantic faculty meeting was planned along very sound lines, as is indicated by the Table of Contents, which outlines the topics considered. The chapters are "Objectives of Teaching," "Teaching in Specific Disciplines," "Teaching Procedures," "Interrelationships of Pathology, Microbiology and Genetics," "The Student," and, finally, "The Teacher." Not only in the text itself but in the extremely useful appendix there is ample testimony to the individuality of physicians and the demonstration that teaching can be done adequately, indeed excellently, in a great variety of ways. These must be determined not only by what is philosophically wise and proper but also what is practical under the individual circumstances of each college of medicine. Still more important, they must be within the range as well as the wishes of each individual teacher.

Reading through the discussions, it appears that perhaps the most useful purpose of such teaching institutes is to demonstrate that there is not necessarily just one single way of doing teaching. Many ways will work. Not the least value of the faculty meeting is to find out what the other fellow is thinking about. This was done on a large scale at this teaching conference. One senses that the majority of the people corralled into this apparently artificial "omnium-gatherum" were skeptical if not in downright revolt. Part of this no doubt resided in the uneasiness which scientists encounter when they deal with subjective material. One outstanding and somewhat

surprising result of the forum was a realization that so much in teaching eludes accurate objective description and partakes more of the transcendental and intangible. If it did nothing more than give teachers in a number of related but not overlapping fields an opportunity to ventilate some of their own feelings and obtain many different points of view it served its purpose. The emphasis seemed to run to individuality and individualism; to excellence in performance without stereotyped teaching; to a dynamic rather than a static concept of the fields under consideration. This was true in spite of the fact that some of the fields are thought to have a good deal of the fixed or static about them. In the warmth generated by sharing different points of view arose the realization that problems in all schools have certain common themes repeated with infinite variations. The knowledge that the problems of teaching were being faced energetically and with a mind open to innovations, as well as with a sound observation of what were basic principles in education, produced what one of the participants called "a reaffirmation of faith in the teaching of medicine." This book is a useful carminative for those grown flatulent in complaining of the *status quo*, being fretful of what medical schools are doing, and being annoyed about the deterioration of undergraduate students, and their teachers, a myth which has gained wide but not alarming currency.

WILLIAM B. BEAN, M.D.

Shock and Circulatory Homeostasis: Transactions of the Third Conference, Sept. 14-16, 1953, Princeton, N. J. Edited by Harold D. Green, M.D. Price, $3.50. Josiah Macy Jr., Foundation, 16 W. 46th St., New York 36, 1955.

The contents of this volume are of specialized physiological interest, dealing about equally and comprehensively with the whole series of cardiovascular reflexes (carotid sinus, chemoreceptor, aortic, coronary, atrial, ventricular, pulmonary, extravagal) that control the circulation and with the physical functional properties of blood vessels, as illustrated in pressure volume experiments on venous systems. The first chapter, however, describes vascular responses, including shock in wounded men in the Korean war.

The presentation is in the usual Macy Conference style, with numerous and interesting interpolations by the participants from this country and abroad.

LOUIS LEITER, M.D.

Ion Exchange and Adsorption Agents in Medicine: The Concept of Intestinal Bionomics. By Gustav J. Martin, Sc.D. Price, $7.50. Pp. 333. Little, Brown & Co., 34 Beacon St., Boston 6, 1955.

The rapid development of ion-exchange resins in recent years and their increasing medical applications make this volume a timely one. It contains introductory chapters on the general theory of ionization and on the biochemical uses of ion-exchange resins. The major part of the book is devoted to clinical applications in peptic ulcer, the edematous states, and toxic disturbances of the gastrointestinal tract. For completeness of discussion the author also reviews the gastrointestinal effects of nonresinous ion-exchange and adsorption materials such as charcoal, kaolin, magnesium, aluminum, etc. In addition, there is a chapter on chelating agents.

In the preface the author expresses his belief that the etiology of all chronic degenerative disease involves absorption from the intestine of small quantities of toxic chemicals. He develops this concept throughout the book and holds out the promise of a possible "conditioning" of the gastrointestinal tract by ion-exchange and adsorption materials. In short, Metchnikoff was correct in his major premise but not as to detail. The available evidence scarcely permits enthusiastic reception of the author's modernized version of the theory of autointoxication. It should also be noted that the therapeutic applications of ion-exchange resins have fallen somewhat short of original expectations.

With these reservations in mind, this book can be read with profit.

LOUIS LEITER, M.D.

Of Research People. By George E. Burch, M.D. Price, not given. Pp. 56, with 40 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

This provocative little book, which can be read through in less time than a television program requires, is the presidential address of Dr. Burch at the January, 1955, meeting of the Southern Society for Clinical Research. Since at least half the space is taken up by cartoon illustrations, one of which appears on the cover, the casual browser may mistake the small volume for a medical "funny book." The cartoons are effective, and, if shown on slides as the author gave his address,

may have helped hold the attention of his audience and nail down his points. What the author has to say is serious and is stated with sufficient clarity and brevity to hold the attention of most readers. It seems unfortunate that cartoons take up so much of the book.

"Research," which seems to mean so many different things to different people, has become a very important activity among institutions of higher learning, government departments, biological houses, and money-dispensing agencies and is now regarded as something different from the everyday activity of the practicing physician and medical school faculty member. It is time some definitions were given and the wheat separated from the chaff. This Dr. Burch has tried to do in simple language. If he makes himself understood, many pseudoinvestigators and "fringe" scientists will find themselves deflated. True investigators will find in the treatise a source of solace and hope. Whether the illustrations hinder or help the reader to comprehend what Dr. Burch is trying to say can not be predicted by me, but I can assure the reader that the short time required to read this thoughtful critique of what now goes on in medical laboratories and administrative offices will be time well spent.

PAUL S. RHOADS, M.D.

Preventive Medicine in World War II: Vol. II, Environmental Hygiene. Editor in Chief, Col. John Boyel Coates Jr. (MC), U. S. Army; Editor for Preventive Medicine, Ebbe Curtis Hoff, Ph.D., M.D. Price, not given. Pp. 404. Medical Department, U. S. Army, Washington 25, D. C., 1955.

This volume provides an excellent review of the methods employed in establishing environmental sanitation under field conditions. The fact that failures have been discussed along with successes makes the volume more valuable for those likely to be concerned with the subject matter.

The sections on waste disposal, control of insects, and rodent control are particularly valuable to the civilian epidemiologist or sanitary engineer, since many useful agents and methods are discussed.

HARRY B. HARDING, M.D.

Practical Endocrinology. By Lewis M. Hurxthal, M.D.; A. Seymour Parker, M.D., and Hirsh Salkowitch, M.D. Price, $7.00. Pp. 318. McGraw-Hill Book Company, Inc., 330 West 42nd St., New York 36, 1955.

This is one of a series of handbooks intended for the busy general practitioner who has no time to read the larger texts or, perhaps, even the beautiful pharmaceutical pamphlets. It is intended to bring him up to date on progress in clinical medicine on the practical side without wasting space on theory. The material is, therefore, boiled down to essentials, and there is no embellishment by bibliography. The author has had wide experience in endocrinology.

The contents include all the major endocrine disorders with the exception of diabetes mellitus. There is an excellent introductory chapter on normal growth and development of children and on the changes produced by pituitary and adrenal disorders. The remainder of the book deals with the diagnosis and treatment of endocrine disturbances of adults. By and large, these are well covered, although at times in a rather sketchy way; for example, the discussion of thyroid diseases includes no mention of the use of cortisone in malignant exophthalmos or of the spuriously high radioiodine uptake by the thyroid in patients on low-salt diets. The treatment of the crises of adrenal cortical insufficiency is scarcely mentioned. On the other hand, the chapters on gonads, on the use of adrenal steroid hormones in rheumatoid arthritis and other collagen diseases, on acromegaly and selective pituitary deficiencies, and hirsutism are well done.

The last part of the book contains detailed instructions on office laboratory tests for the interested physician. It is questionable on a practical basis whether urinary 17-ketosteroid assays should be included. In general, the stated purpose of the author has been fulfilled, and the general practitioner who reads this volume carefully in relation to specific clinical problems will derive a satisfying amount of practical information.

LOUIS LEITER, M.D.

Splenin A in Rheumatic Fever: The Testing of Splenin A as an Anti-Inflammatory Agent. By Alvin F. Coburn, M.D.; Lucile V. Moore, M.D.; Judith Wood, M.D., and Mary Roberts, R.N. Price, $2.75. Pp. 86, with 5 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

The clinical observation of an exacerbation of rheumatic fever occurring rapidly after splenectomy led to the extensive research described in this volume. The author's work in America has been correlated with other work in Britain and Canada and has led to clinical trials. Two

substances are believed to be produced by the spleen. The first, called splenin A, appears to exert an anti-inflammatory action, whereas the second, called splenin B, appears to aggravate inflammation. These investigators have given splenin A intravenously or intramuscularly to 47 patients under the age of 14 with rheumatic fever in two Chicago hospitals. In the acute attack each patient was watched by several physicians and had three serological tests (AS titer, ESR, and serum diphenylamine reaction) carried out at regular intervals. Patients were watched for exacerbation of the disease after the withdrawal of the drug splenin A, and a follow-up of one to three years was carried out. The patients were treated in three different groups with various batches of splenin A. The controls were not concurrent. A subsidence of symptoms was noted about 48 hours after the drug was started. A few patients showed exacerbations while on the drug, but the vast majority showed gradual and continued improvement, which, however, was less obvious than that observed with corticotropin. It was found that there was no advantage to the intravenous route of administration. No cardiac dilation or tachycardia occurred during treatment, and clinical recovery occurred in all except one, who subsequently did not respond to either salicylate or corticotropin. A minimum therapeutic daily dose was established.

This record of a period of clinical research illustrates many of the difficulties incumbent on this method. The authors have gained their objective of demonstrating that splenin A has an anti-inflammatory action on the manifestation of rheumatic fever. They have been greatly handicapped by the expense and difficulty in preparation of the material used. One feels, however, that more use might have been made of the material had greater consideration been taken of the initial planning of this study. This is a volume of great interest to those working in the field of rheumatic fever. It will also appeal to many people working in diverse fields of infectious disease. It is probably only a beginning in this subject which may in the future offer great advances in the fundamental knowledge of inflammation, and it is a useful source of references on the work on splenin A to date.

J. MACLEAN SMITH, M.D.

Office Procedures. By Paul Williamson, M.D. Price, $12.50. Pp. 412, with illustrations. W. B. Saunders Company, 218 Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

The general practitioner is daily confronted by an unpredictable variety of clinical problems demanding prompt disposition. To provide assistance, the author has recorded those office procedures of proved value culled from his experience and that of two colleagues. No attempt is made to provide an encyclopedia of all methods by which a given task may be accomplished. In the fifteen sections, which surprisingly well cover the considerable gamut of general practice, notes, tables, and understandable diagrams are included. The included remarks relevant to the art and philosophy of the practice of medicine will be of limited interest to some readers.

Particular and needed emphasis is placed on the importance of gentle technique in performance of minor surgical procedures, the recognition of which patients require hospitalization and should not be cared for in the office, and the remembrance of the socioeconomic factors of which one should be mindful. Arterial and nerve suture, removal of foreign bodies, and fractures are discussed in proper reference to hospital care. The sections concerned with office laboratory methods, bacteriology, diagnosis of vascular and neurological disorders, bandaging, common diagnostic roentgen problems, and local anesthesia techniques should prove especially valuable. The text, which is readable, surprisingly well organized in view of the diffuseness of the subject, and well indexed, could have been shortened and improved by eliminating verboseness and ambiguity and unnecessarily elementary sentences. Some readers will find themselves in disagreement with the management of the patient with late cervical carcinoma, varicose veins, breast masses, and hemorrhoids which is advocated. This book will be of considerable value to the general practitioner as a practical tool to assist in his practice and, to a much less degree, to the intern or resident dealing with outpatients.

JOSEPH A. BUCKWALTER, M.D.

Nutritions in Infections. Edited by Roy Waldo Miner, M.D., Conference Chairman, and Consulting Editor W. Alan Wright. Price, not given. Pp. 173, with many illustrations. Annals of the New York Academy of Sciences, 2 East 63d St., New York 21, 1955.

The logical inference that there must be some connection between the nutritional state of the host and the susceptibility and reaction to infections has led to a great deal of work. Much of it is far short of definitive. Some is contradictory and confusing. Even the most faint-hearted

believer in the importance of an ecological approach to disease who knows the intricacies of multiple causality can get little encouragement from reading most of the articles in this symposium. The contributions of Axelrod, Horwitt, and Kinsell, based on their long, painstaking, and critical studies, set a high level of performance, which unfortunately is not reached in other papers. The bleak eye of a skeptic finds too many papers proposed as scientific studies which do no credit to their enthusiastic and uncritical authors. It is melancholy to read even one paper presenting wholly unconvincing data and drawing sweeping conclusions. Here we have a whole parade of them. It would appear that the symposium had been thought up by enthusiastic cavaliers of polytherapy anxious to find testimony to support the sales of an "omnium gatherum" of antibiotics and vitamins. Panacea is announced in the form of a therapeutic hodgepodge which it will take years to evaluate in any critical sense.

Several of the papers report work quite obviously directed not so much by primary ideas as by having available a compound to test. Evidence that vitamins add anything to the therapeutic virtue of antibiotics is not supported by the data. Project research is at its very worst when directed by and beholden to the concoctors of therapeutic combinations. To have it set the tone for a whole symposium is discouraging. Science and research must be directed by the curiosity of the investigator rather than by the pleasure or profit of a granting agency. As Schneider says in his happy epilogue, curiously out of tune with the rest of the papers, the separate disciplines of nutrition and infection will have to come together much more closely before sound fact and demonstration emerge from the mass of hypothesis and inference comprising so much of the material in this symposium. Hypothesis is a magnificent aid in advancing science as long as it is recognized that to repeat it over and over does not establish it as a fact. Unfortunately, the clinical science of nutrition has not had anything like the rigorous and critical attention paid to many aspects of infection. Until the coming of a new group of investigators competent in the two fields simultaneously or until a new critical spirit rises up from our present state of confusion we are likely to be led around by enthusiasts whose wishful thinking and often perfectly logical ideas lead them into some of the clinical cul-de-sacs exemplified in this extremely uneven symposium.

WILLIAM B. BEAN, M.D.

Clinical Pathologic Conferences of Cook County Hospital. Edited by Hans Popper, M.D., Ph.D., and Daniel S. Kushner, M.D. Price, $5.00. Pp. 325. McGraw-Hill Book Company, Inc., 330 West 42nd St., New York 36, 1955.

This volume reflects the philosophy and methods of the clinical pathological conferences of the Cook County Hospital, in Chicago. There is an excellent historical introduction on the growth of this teaching technique and on the advantages of the multidisciplinary approach. The cases selected are limited to three groups—cardiac, vascular, and renal.

In the cardiac group there are cases of heart failure due to unusual myocardial degeneration, cyanotic congenital heart disease, silicosis with cor pulmonale, hypertensive heart disease with rupture of the aorta as a result of medial necrosis, left ventricular aneurysm, and tuberculous pericardial effusion. The vascular cases include sickle-cell anemia with thromboses, thrombocytopenic purpura with endocrinopathy, diffuse lupus erythematosus, atypical periarteritis nodosa, and pulmonary fibrosis with scleroderma. The renal group includes renal amyloidosis in rheumatoid arthritis, pyelonephritis and pyonephrosis with amyloidosis, fulminating acute glomerulonephritis, malignant hypertension, polycystic kidneys, diffuse glomerulonephritis with parathyroid hyperplasia and metastatic calcification, Addison's disease with shock and ischemic nephropathy, and lipoid nephrosis complicated by mercurial nephrosis.

The individual cases usually represent the rarer and more complicated types, but they lend themselves well to discussion of the general aspects of differential diagnosis, pathology, and pathogenesis. As might be expected, the level of excellence of the discussion varies from case to case, but on the whole, it is interesting and fairly comprehensive from both the clinical and the pathologic standpoint. However, there is not enough emphasis on physiological mechanisms in cardiovascular diseases, nor on the bacteriological and immunological aspects of renal diseases, in which there have been considerable recent advances.

On the whole, this volume will furnish interesting reading to the physician who will take the trouble to puzzle over the details of the clinical cases. There is a brief bibliography at the end of each exercise, and often a supplementary note by the editors in which concepts as to pathogenesis, pathology, or other special features are brought up to date. The illustrations are carefully selected and well reproduced.

LOUIS LEITER, M.D.

The Clinical Care of the Diabetic. By James J. Short, M.D., F.A.C.P. Price, $3.95. Pp. 84. San Lucas Press, 316 N. Bailey St., Los Angeles, 1955.

This is a well-written booklet, but, unfortunately, it is all too limited a discussion of a complicated subject. The author deals briefly with the etiology, pathology, and diagnosis of the disease and has a good section on the treatment of diabetic acidosis and coma. Juvenile diabetes, surgical conditions, hygiene, and pregnancy are touched upon as well as the use of the various insulins. Diet charts are included in the longest section, on treatment of uncomplicated adult diabetes.

In the author's own words, the work is meant only as a "guide to the clinician in the treatment of diabetes." It is not intended as an original work, and there is no bibliography. Newer concepts of insulin usage are not included. In spite of its brevity, there is an abundance of sound advice.

JOHN C. FARMER, M.D.

Pathology Seminars. Edited by Robert S. Haukohl, M.D., and W. A. D. Anderson, M.D., with contributions by L. V. Ackerman, M.D.; A. C. Allen, M.D.; Col. J. E. Ash, M.D.; A. P. Stout, M.D., and R. A. Willis, M.D. Price, $10.00. Pp. 195, with 131 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1955.

The "slide seminar" has become an increasingly popular and stimulating method of postgraduate teaching in pathology. The participants and discussant study slides and histories of a group of appropriate cases, submit their diagnoses in advance, then discuss the clinical and pathological features in an informal way.

This small book is a collection of "slide seminars" given at Marquette University School of Medicine by various distinguished pathologists. Dr. Ackerman's cases include tumors of the lung, salivary gland, rectum, notochord, breast, and parathyroid. Dr. Allen discusses various lesions of the skin. Dr. Ash chooses cases representing clinical entities in the nose and throat. Dr. Stout's cases are principally soft-tissue tumors, and Dr. Willis discusses a number of interesting tumors.

All of the discussions are of the high quality that might be expected from such an eminent group. The line of reasoning leading to the diagnosis is clearly shown in each case, and the differential diagnosis is carefully considered. The emphasis is on the practical problems which arise in the everyday practice of pathology, even though some of the lesions are uncommon. The photomicrographs are excellent.

This book is easy to read and of considerable interest. It might be even more stimulating if the diagnosis were presented at the end rather than the beginning of each discussion, reproducing the actual situation at the seminar, and giving the reader an opportunity to participate, even though vicariously, in the conference.

J. C. SHERRICK, M.D.

Administrative Medicine: Transactions of the Third Conference October 6, 7, and 8, 1954. Edited by George S. Stevenson, M.D. Price, $3.00. Pp. 172. Josiah Macy, Jr. Foundation Publications, 16 West 46th St., New York 36, 1955.

This brief volume presents the transactions of the Third Conference of the Administrative Medicine series sponsored by the Macy Foundation. The meritorious effort to preserve the spirit of informal discussion in reporting this "working conference" at times unfortunately degenerates into quibbling over trivia. The major discussions center about medical administration as related to hospital administration.

The presentation concerning the distinctive characteristics and educational requirements of the medical administration, introduced by Anthony J. J. Rourke, is refreshingly forthright. Hugh Leavell somewhat facetiously remarks that "someone pointed out that the medical administrator must be a mental cosmopolitan, that he must deal with the multiple services provided under his supervision, with the multiple supervision which he himself has, and he must be governed by incentives other than the profit motive, under conditions of limited competition." Dr. Ray E. Trussell's paper describing the Hunterdon County Medical Center project will be invaluable to those interested in this bold, imaginative approach to the hospital in its relationship to the community.

The book will prove informative and at times provocative to medical administrators in general and hospital administrators in particular.

R. H. Y.

Einführung in die biologische Registriertechnik. By Dr. Med. Herbert Klensch. Price, $7.85. Pp. 222, with 142 illustrations. George Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1954.

The author reviews recording techniques as used in physiologic and clinical experimentation. There are ten chapters. They extend from a description of a simple kymograph, a photocell, a flow-meter, and a plethysmograph to electronic equipment. They include electrocardiography, electroencephalography, and the various means of producing electric stimulation of biologic objects.

In about 200 pages the treatment of so many apparatuses and their application is, of course, brief and cursory. However, the book will serve well as a source of basic information. The language is simple and clear. References are almost entirely German.

K. HARPUDER, M.D.

BOOKS RECEIVED

VA Medical Monograph: A Follow-Up Study of World War II Prisoners of War. By Bernard M. Cohen, Ph.D., and Maurice Z. Cooper, M.D. Price, $1.50. Pp. 81, with 43 tables and 5 charts. U. S. Government Printing Office, Washington 25, D. C., 1954.

Diseases of the Liver. Edited by Leon Schiff, M.D., Ph.D., with 28 contributors. Price, $16.00. Pp. 738, with 245 illustrations and 45 tables. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1956.

CIBA Foundation Symposium: Experimental Tuberculosis; Bacillus and Host; Addendum on Leprosy. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. Price, $9.00. Pp. 396, with 69 illustrations. Little, Brown & Company, 34 Beacon St., Boston 5, 1955.

Practitioners' Conference Held at The New York Hospital-Cornell Medical Center. Vol. 3. Edited by Claude E. Forkner, M.D., F.A.C.P. Price, $6.75. Pp. 293, with 26 illustrations and 2 tables. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1956.

The Year Book of Drug Therapy (1955-1956 Series). Edited by Harry Beckman, M.D. Price, $6.00. Pp. 560, with 64 illustrations and many tables. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

Ergebnisse der medizinischen Grundlagenforschung. Edited by K. Fr. Bauer, with several contributors. Price (DM 129), $30.75. Pp. 856, with 217 illustrations and 379 tables. Georg Thieme, Herdweg 63, (14a) Stuttgart, 1956.

Your Blood Pressure and How to Live with It. By William A. Brams, M.D. Price, $2.95. Pp. 160, with 7 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1956.

VA Medical Monograph: Tuberculosis in the Army of the United States in World War II. By Esmond R. Long, M.D., and Seymour Jablon, A.M. Price, $1.50. Pp. 88, with 56 tables and 15 charts. U. S. Government Printing Office, Washington 25, D. C., 1955.

Report of the Seventeenth Ross Pediatric Research Conference: Growth and Development of Dental and Skeletal Tissue; Clinical and Biological Aspects. Edited by Samuel J. Fomon, M.D.; Warren R. Sisson, M.D., Chairman. Price, not given. Pp. 78, with 22 illustrations. Issued by Ross (formerly M and R) Laboratories, Columbus 16, 1956.

Shock and Circulatory Homeostasis: Transactions of the Fourth Conference, December 6, 7 and 8, 1954. Edited by Harold D. Green, M.D. Price, $5.00. Pp. 291, with 69 figures and 26 tables. Josiah Macy, Jr. Foundation Publications, 16 West 46th St., New York 36, 1955.

Disease of the Endocrine Glands. By Louis J. Soffer, M.D., F.A.C.P. Second edition. Price, $16.50. Pp. 1032, with 102 illustrations and 3 color plates. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

Diseases of the Chest. By H. Corwin Hinshaw, M.D., Ph.D., and L. Henry Garland, M.B., B.Ch. Price, $15.00. Pp. 727, with 634 illustrations on 277 figures. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

A Modern Pilgrim's Progress for Diabetics. By Garfield C. Duncan. Price, $2.50. Pp. 222, with 15 illustrations, 2 tables, and 2 charts. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Clinical Electrocardiography: I. The Arrhythmias. By Louis N. Katz, M.D., and Alfred Pick, M.D. Price, $17.50. Pp. 738, with 415 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

Excitability of the Heart. By Chandler McC. Brooks, Ph.D.; Brian M. Hoffman, M.D.; E. E. Suckling, M.Sc., M.E.E., and Oscar Orias, M.D. Price, $6.50. Pp. 373, with 87 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, 1955.

Clinical Management of Renal Failure. By Maurice B. Strauss, M.D., and Lawrence G. Raisz, M.D. Price, $2.75. Pp. 115 with 2 charts. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Clinical Laboratory Diagnosis. By Samuel A. Levinson, M.S., M.D., Ph.D., and Robert P. MacFate, Ch.E., M.S., Ph.D. Fifth edition. Price, $12.50. Pp. 1246, with 244 illustrations, 142 tables, 13 plates (11 in color). Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

Hypertension: A Manual for Patients with High Blood Pressure. By Irvine H. Page, A.B., M.D. Second edition. Price, $3.00. Pp. 109, with 8 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Annual Review of Physiology. Edited by Victor E. Hall. Price, $7.00 (foreign, $7.50). Pp. 591, with 1 illustration. Annual Reviews, Inc., Stanford, Calif., 1956.

Prüfung der körperlichen Leistungsfähigkeit. By Doz. Dr. Med. Habil Volkmar Böhlau. Price, DM 13.50. Pp. 91, with 48 illustrations. VEB Georg Thieme, Hainstrasse 17-19, Leipzig C 1, Germany, 1955.

News and Comment

ANNOUNCEMENTS

Postgraduate Seminar on Diagnosis and Therapy.—The Mount Sinai Hospital of Greater Miami announces the Sixth Annual Postgraduate Seminar on Recent Advances in Diagnosis and Therapy, to be held at the Fontainebleau Hotel, Miami Beach, Fla., May 17-20, 1956.

The seminar will be conducted by a group of ten lecturers: Drs. Alexander Brunschwig, Cornell University; Joseph Bunim, National Institute of Arthritis and Metabolic Diseases; George Crile Jr., Cleveland Clinic Foundation; Robert Greenblatt, Medical College of Georgia; Keith S. Grimson, Duke University; Louis Leiter, College of Physicans and Surgeons, Columbia University; William F. Reinhoff Jr., Johns Hopkins Hospital; Hans Selye, University of Montreal; Solomon Silver, Columbia University; Edward Weiss, Temple University Medical School.

The fee for the course is $20.00. Applications may be mailed to the Seminar Committee, Mount Sinai Hospital of Greater Miami, Miami Beach, Fla.

Regular Corps Examinations for Medical Officers, U. S. P. H. S.—A competitive examination for appointment of Medical Officers to the Regular Corps of the United States Public Health Service will be held in various places throughout the country on June 12, 13, 14, and 15, 1956.

Appointments provide opportunities for career service in clinical medicine, research, and public health. They will be made in the ranks of Assistant and Senior Assistant, equivalent to Navy ranks of Lieutenant (j. g.) and Lieutenant.

Entrance pay for an Assistant Surgeon with dependents is $6017 per year; for Senior Assistant Surgeon with depenedents, $6918. Qualified officers are promoted at regular intervals.

Benefits other than promotions include periodic pay increases, 30 days annual leave, sick leave, medical care, disability retirement pay, regular retirement pay which is three-fourths of annual basic pay at time of retirement, and other privileges.

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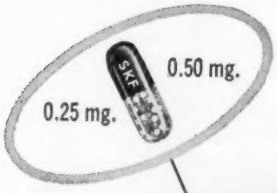
Requirements for both ranks are U. S. citizenship, age of at least 21 years, and graduation from a recognized school of medicine. For the rank of Assistant Surgeon, at least seven years of collegiate and professional training and appropriate experience are needed. For Senior Assistant Surgeon, an additional three years, for a total of at least ten years of collegiate and professional training and appropriate experience, are required.

Entrance examinations will include an interview, physical examination, and comprehensive objective examinations in the professional field.

Application forms may be obtained from the Chief, Division of Personnel, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C. Completed application forms must be received in the Division of Personnel no later than April 30, 1956.



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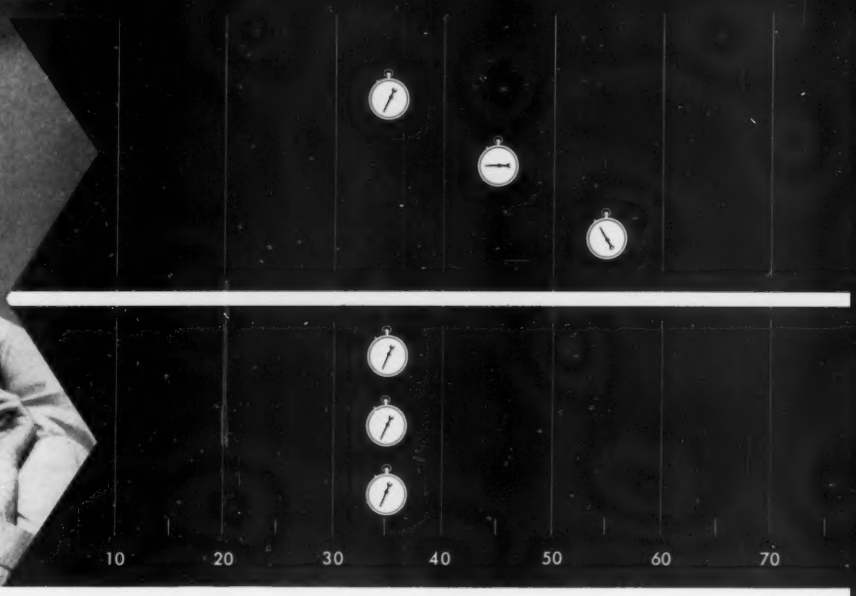

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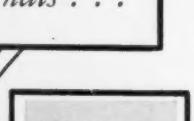

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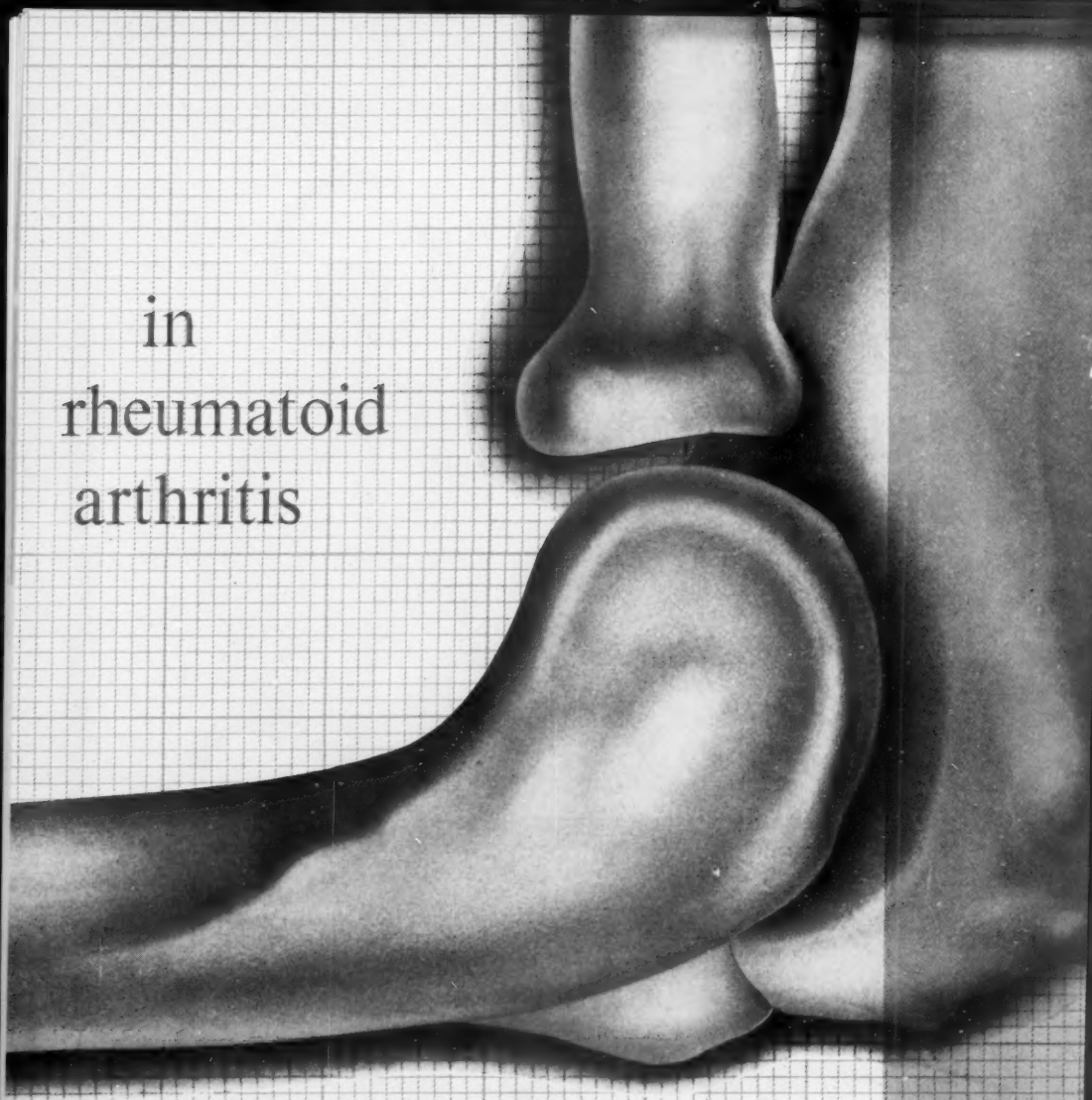

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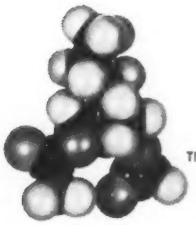

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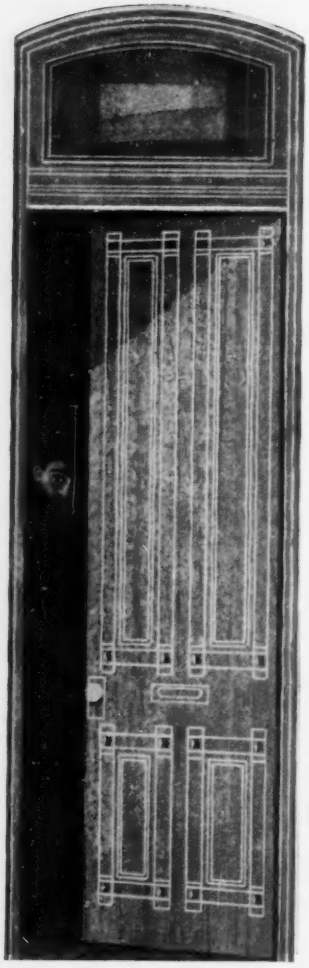

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